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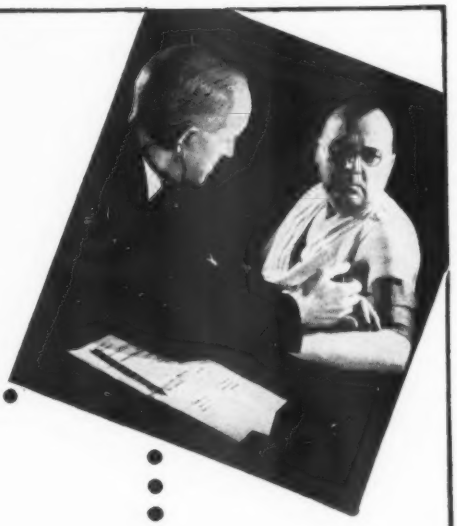

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1949

ORIGINAL ARTICLES

OBSERVATIONS ON PENICILLIN-TREATED CARDIOVASCULAR SYPHILIS*

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There have been only a few reports in the literature on the effect of penicillin in a significantly large number of patients with late cardiovascular syphilis. An important reason for this is the fact that many clinicians have been reluctant to use so potent a spirocheticidal agent in patients with syphilitic heart disease because of the fear of inducing a serious Herxheimer reaction and also because of the possibility of too rapid healing resulting in the so-called therapeutic paradox. This is a carry-over from the pre-penicillin days when it was the rule in most clinics to prepare all patients with cardiovascular syphilis with a preliminary course of bismuth or mercury before administering the more potent arsenicals.

Rather early in the penicillin era Dolkart and Schwemlein[3] described 2 patients with aortic regurgitation who experienced untoward reactions while under penicillin therapy. One of the patients developed severe attacks of angina and ventricular extrasystoles soon after treatment was started. The second experienced intermittent substernal pain after 700,000 units of penicillin. Callaway and his group[2] reported as a possible illustration of therapeutic paradox, a patient who suffered the rupture of an aortic cusp several weeks after completion of penicillin therapy.

Moore, in his recent monograph,[7] reported on 12 cases of active cardiovascular syphilis which had been treated with penicillin at the Johns Hopkins Hospital. These patients had aortic regurgitation, aneurysm, or syphilitic aortitis with coronary osteal stenosis and angina of effort. Six of the patients also had neurosyphilis. In each case

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With collaboration of John H. Stokes, M.D., Edwin N. Hesbacher, M.D., George D. Gammon, M.D., Herman Beerman, M.D., Norman R. Ingraham, Jr., M.D. and John W. Lentz, M.D., and the technical assistance of Verna Mayer Stein, Emily Stannard, Jane Barbara Taylor, R.N., and Mildred F. Wills, R.N.

penicillin was started in very small dosage and then gradually increased over a period of days in an effort to avoid a Herxheimer reaction. There was one possible instance of therapeutic shock in this series of cases. This was in a patient who died on the fourth day of combined fever (malaria) and penicillin therapy. The autopsy revealed multiple plaques of syphilitic aortitis with fresh hemorrhages. The period of post-treatment observation in Moore's cases was too short to report on the therapeutic effect. One of the patients with a large aneurysm of the thoracic aorta died of rupture of the aneurysm 6 months after completion of treatment.

There is some doubt now that reducing the initial penicillin dosages actually prevents the occurrence of Herxheimer reactions since they have been observed following small doses. Olansky[8] recently reported on 6 patients (4 infectious syphilis and 2 late syphilis) in each of whom initial injections of 1,000 Oxford units of penicillin produced a febrile Herxheimer reaction. Incidentally, in this report Olansky reiterates the belief that penicillin even in small doses should not be administered to patients with late or complicated syphilis until a course of bismuth has been given. Stokes and Steiger[11] found that a reduction of the initial dosage to 500 units in early infectious syphilis was not sufficient to prevent Herxheimer reactions.

Russek and his co-workers[10] treated 15 patients with syphilitic aortitis, including 4 cases of aortic aneurysm, with relatively large doses of penicillin —40,000 units every 2 hours for 85 doses. Their paper deals principally with the incidence of reactions; the follow-up period of 1 to 3 months was too short to evaluate the efficacy of the treatment. Only 1 patient suffered an untoward reaction which might have been attributed to penicillin—relatively mild substernal pain which disappeared despite continuance of penicillin. In 4 patients it was felt that there was definite improvement in coronary reserve manifested by decrease of substernal pain on exertion. Electrocardiographic improvement did not occur. These workers conclude, on the basis of these observations, that the risk of untoward reactions from penicillin in cardiovascular syphilis is small. They also maintain that the small risk entailed may be justified by the therapeutic results obtained.

Tucker and Farmer[12] have recently reviewed 34 cases of cardiovascular syphilis which were treated with penicillin: 25 had aortic insufficiency and 9 had saccular (thoracic) aortic aneurysms. These patients were started on treatment with dosages ranging from 500 to 100,000 Oxford units every 3 hours. The total dosages varied from 2 million to 15 million Oxford units. Five of the patients experienced febrile reactions early in the course of treatment (one of these after an initial dose of only 500 units), and 2 patients who had been having anginal attacks continued to have them during and following the administration of penicillin. In no case was it felt necessary to interrupt the penicillin therapy. The authors postulate that the febrile reactions which occurred in their cases may have been related to the concomitant neurosyphilis which each of these patients had. They conclude: "The absence of reported severe reactions proved to be due to treatment with penicillin tends to confirm our impressions that the dangers of severe untoward reactions may have been unduly emphasized."

Method of Study. This report is based on a study of 50 patients with cardiovascular syphilis who were admitted to the Institute for the Study of Venereal Disease between 1943 and 1948 (Table 1.)

In the beginning cardiac studies included a physical examination, orthodiagram, and a pre-penicillin electrocardiogram. Later, when it was found that in patients with early infectious syphilis there were electrocardio-

graphic abnormalities which showed changes during penicillin therapy, it was decided to have the records repeated at approximately 3 day intervals during the course of treatment to determine if changes also occur in late cardiovascular syphilis. Six patients in congestive failure were under digitalis during the course of penicillin therapy; this was considered in interpreting their electrocardiograms.

Forty of the 50 patients had received metal chemotherapy previously. However, most of them had received no antisyphilitic treatment for several years and only 4 patients in the entire group had had any treatment within a period of 3 months prior to the administration of penicillin.

some 15 of the patients were started with doses of 40,000 to 80,000 Oxford units every 2 hours.

Results. AORTITIS. There were 23 patients with uncomplicated syphilitic aortitis. We are cognizant of the fact that the clinical diagnosis of uncomplicated syphilitic aortitis is often a very difficult one, especially in the presence of hypertension and, or, arteriosclerosis. However, only those patients in whom the evidence for aortitis (especially fluoroscopic) was marked were included in the study.

TABLE 1.–DATA PERTAINING TO 50 PATIENTS WITH CARDIOVASCULAR SYPHILIS

	No. Cases	Age	Sex M	Sex F	Race W	Race N	Ht. enlarge or hypert.	Cardiac symptoms	Ttl. No.	No. of patients on whom ECG were made: Before Abnormal ECG	During ECG Ttl. No.	During ECG Changes	After* Ttl. No.	Therapeutic shock (Herxheimer)	Treatment stopped because of symptoms
Aortitis	23	26 to 69	15	8	13	10	9	2	23	6(a)	11	3	16	4(b)	0
Aortic insuff.	20	38 to 66	19	1	12	8	18	8(c)	20	11	13	2	13	3(d)	0
Aneurysm	5	47 to 67	4	1	2	3	3	2	5	1(e)	2	1	4	1?(f)	0
Aneurysm & aortic insuff.	2	43 to 69	2	0	1	1	0	2(g)	2	1	2	2	1	1?(h)	0

(a) Probable ancient posterior infarction in one.
(b) All febrile.
(c) Marked congestive failure in five.
(d) All febrile.
(e) History of posterior infarction in one.
(f) Precordial constriction on third day of treatment.
(g) Congestive failure in one.
(h) Had recurrent attack of cardiac asthma on third day.
* ECG changes not listed as they are still being followed up.

All of the patients were given sodium penicillin in aqueous solution on a round-the-clock schedule. In the early days the crude amorphous substance was used and, when it became available, crystalline penicillin-G. The total penicillin dosages ranged from 1,200,000 to 9,600,000 Oxford units. At first, all patients with cardiovascular syphilis were started on small doses (500 to 5,000 units every three hours for the first 24 to 48 hours) and gradually increased over a period of several days until a dose of 40,000 to 80,000 Oxford units every 2 or 3 hours was reached. Later, when it was found that reducing the initial dosage did not necessarily prevent the occurrence of a Herxheimer reaction[8,11]

These patients ranged in age from 26 years to 69 years. The sex and race distribution were as follows: 10 white males, 3 white females, 5 Negro males, and 5 Negro females. Eighteen of the patients also had central nervous system syphilis, 1 had a gumma of the lip, and 1 had diabetes mellitus. At the time penicillin treatment was instituted 21 of the 23 patients had positive blood serologic tests for syphilis.

The initial penicillin doses ranged from 500 to 80,000 units and the total

dosages from 1,200,000 to 9,600,000 Oxford units.

Only 2 of the 23 patients had experienced cardiac symptoms prior to penicillin therapy; they had complained of paroxysmal dyspnea. Eight were found to have slight cardiac enlargement and 1 moderate enlargement.

Six of the group with simple aortitis had electrocardiographic changes before penicillin. Five showed abnormal T waves in the limb and chest leads. In 1 patient the T waves in Lead I and II, CR_4 and CR_5 were inverted; in 2 patients completed the prescribed course without further untoward reactions.

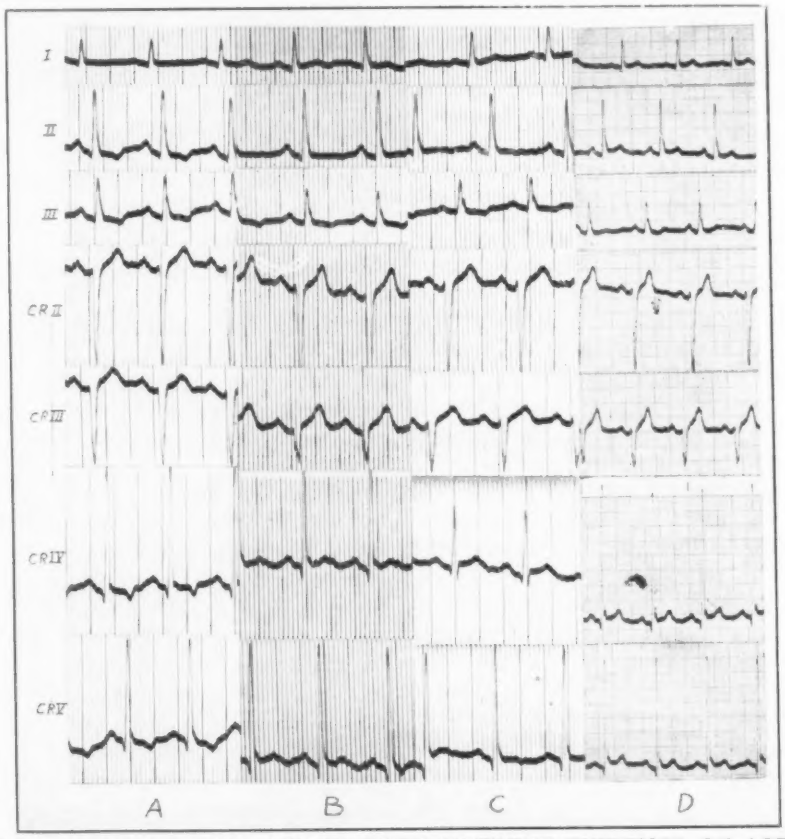

FIGURE 1.—COLORED MAN, AGE 38, WITH DEFINITE EVIDENCE OF AORTITIS.
A. Record made 4-23-47, before penicillin.
B. 4-26-47 after approximately 1.5 million units of penicillin.
C. 4-29-47 after 4.2 million units of penicillin. An electrocardiogram on 5-2-47 was similar to C.
D. 1-3-48 Eight months after penicillin. An ECG on 4-3-48 was similar to D.

Four patients experienced transient temperature rises within 24 hours after penicillin therapy was started. These were interpreted as evidence of Herxheimer reactions. However, in no case was treatment interrupted and all patients the T waves were flat in Lead I, inverted in II and III and abnormal in CR_4 and CR_5; in the fourth the T waves were inverted in II and III, diphasic in $CR_{2,3,4}$ and flat in CR_5; in the remaining case there were flat T waves

in Leads I and CR_5. The sixth abnormal electrocardiogram had deep Q waves in Leads II and III, which suggested a healed posterior infarction. In 3 of the 5 cases showing pre-penicillin T wave changes, electrocardiograms were made during treatment; 2 showed temporary improvement in T waves, but later retrogressed to the pre-penicillin state. The other patient had marked T wave changes before treatment, improved considerably during treatment and continued to show improvement 1 year later (Fig. 1). One patient in whom pre-penicillin electrocardiograms were abnormal (T wave changes) had a normal tracing 4 months after completion of treatment. Unfortunately, electrocardiograms were not made during treatment.

One patient developed angina pectoris, with concomitant electrocardiographic changes ten months after penicillin.

Aortic Insufficiency. There were 20 patients with aortic insufficiency ranging in age from 39 to 66 years. The sex and race distribution were as follows: 11 white males, 8 Negro males, 1 white female. Eighteen also had central nervous system syphilis. All had positive blood serologic tests for syphilis.

Although it has been known that aortitis and its complications are more common in males, the ratio of 19 males to 1 female in our series is unusually high. This is not the result of selection, but actually represents all the individuals with aortic regurgitation who came under our observation.

The initial and total penicillin dosages were the same as those used in uncomplicated aortitis.

Only 3 patients in this group experienced temperature elevations (all within the first 16 hours) after treatment was started, and all completed the prescribed course of therapy.

Eight of the patients had experienced cardiac symptoms prior to penicillin therapy. Three had dyspnea on exertion, and angina pectoris; 1 had an old coronary occlusion. Five of the patients were in congestive failure and required bed rest, digitalis, ammonium chloride, and mercurial diuretics. It is of interest that each of these individuals was given penicillin concomitantly with the measures to correct cardiac decompensation and all of them left the hospital in an improved condition. Although this is admittedly too small a group upon which to base definite conclusions, it suggests that penicillin treatment of cardiovascular syphilis need not be delayed because of cardiac decompensation.

Eighteen of the 20 patients had enlarged hearts. In the 2 whose cardiac silhouettes were within normal limits of size the configuration suggested left ventricular hypertrophy.

In the group of 20 cases of aortic regurgitation, 10 showed significant T wave inversions and 2 had bundle branch block before treatment. Incidentally, 1 of the patients with inverted T waves also had auricular fibrillation; the only important arrhythmia noted in the entire group of 50 cases. In 4 instances T_1 and the T waves of CR_5 were inverted or diphasic; in 4, T_2 was also diphasic or inverted and in 2 the T waves of all limb leads were inverted. Of the cases with bundle branch block, 1 had right bundle branch block (with wide S waves), the T waves in Leads II and III were inverted and the T waves in Leads CR_3, CR_4, and CR_5 were diphasic. The other showed left bundle branch block of the discordant type. One of the patients with T wave changes showed slight electrocardiographic improvement during treatment; subsequently however, the T wave changes became more marked. Another patient who had slight electrocardiographic changes before treatment developed inverted T waves in Leads I, II, and

III, and abnormal T waves in CR_4 and CR_5 during his course of penicillin. A follow-up electrocardiogram made 3 months after treatment showed considerable improvement although the tracing was not normal. Still another patient (Fig. 2) showed abnormal T waves before treatment and marked improvement 5 months later; this was also associated with definite improvement in his general condition.

AORTIC ANEURYSM. There were 5 patients with aortic aneurysm ranging in age from 47 to 69 years. The distribu-

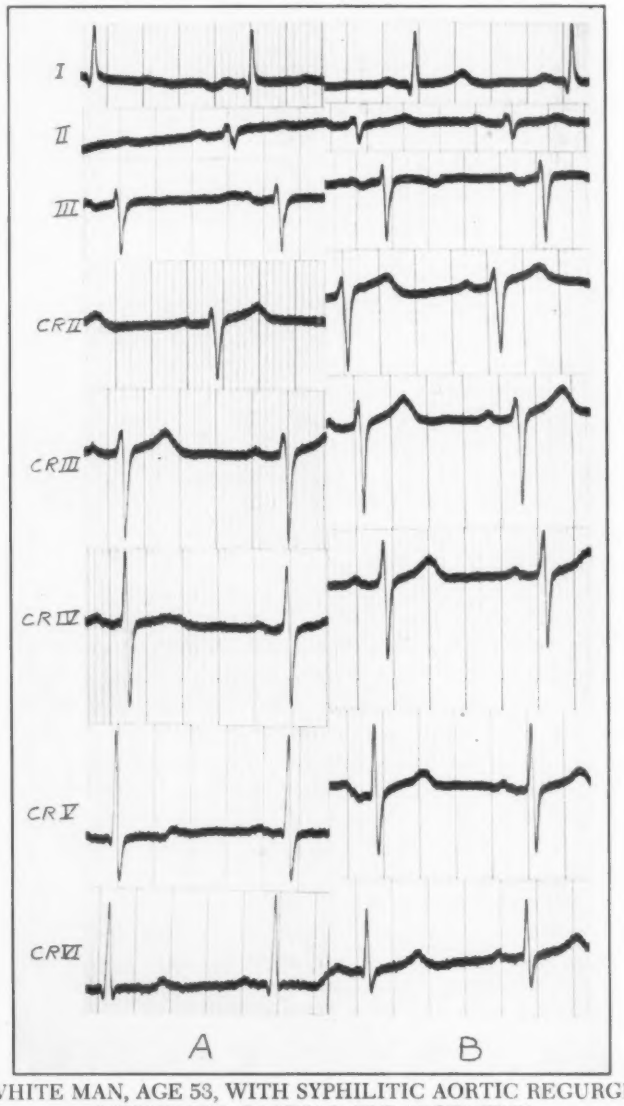

FIGURE 2.–WHITE MAN, AGE 53, WITH SYPHILITIC AORTIC REGURGITATION AND MODERATE CARDIAC ENLARGEMENT.

A. Record made 12-8-45, before penicillin.
B. 5-11-46 after 2,400,000 units penicillin. Electrocardiograms made 4-4-47 and 6-1-48 were similar to B.

tion by sex and race was as follows: 2 white males, 2 Negro males, and 1 Negro female. One patient in the group had central nervous system syphilis. All had positive blood serologic tests for syphilis.

The initial penicillin dosages ranged from 500 to 80,000 Oxford units and the total dosages from 3,600,000 to 9,600,000 units.

None of the patients experienced a febrile reaction during treatment. A 54 year old Negro female complained of slight precordial constriction for several hours on the third day of treatment. According to her history she had experienced no cardiac symptoms prior to the administration of penicillin. She completed the course of treatment without interruption of the schedule.

Three of the 5 patients with aneurysms had enlarged hearts. One patient in the group, who also had hypertension, showed an abnormal electrocardiogram in which there were inverted T waves in Leads II and III and flat T waves in CR_5. These changes became more marked during treatment and have remained so on follow-up, but they were probably in part due to digitalis.

Aortic Aneurysm and Aortic Regurgitation. There were 2 patients with both aortic aneurysm and aortic insufficiency. One was a 43 year old white male, the other a 69 year old Negro male. The former also had central nervous system syphilis with a Type III spinal fluid. Both had positive blood tests.

The older man was admitted to the hospital in marked cardiac failure. There was no definite history of previous antisyphilitic treatment. His failure had been progressive over a period of about 4 years. Penicillin was started in small doses (500 units) on a 2 hour schedule. He had no untoward reactions until the third day of treatment, when maximum dosage was reached (40,000 units every 2 hours). He then experienced an attack of severe substernal oppression and dyspnea similar to those he had on frequent occasions before treatment. Penicillin dosage was reduced from 40,000 to 10,000 Oxford units every 2 hours for the next 48 hours and then increased again to 40,000 units every 2 hours; the patient completed a course of 4,800,000 Oxford units without further untoward reactions. His pre-treatment electrocardiogram revealed flat T waves in the limb leads and slight inversion in $CR_{3,4,5}$. There was slight improvement in the electrocardiograms made on the third and thirteenth days of treatment. On follow-up 4 months after treatment he felt much improved and had experienced only 2 slight attacks of dyspnea. Examination disclosed no signs of congestive failure.

The other patient had experienced dyspnea on exertion and precordial pain before treatment. He denied having received previous antisyphilitic therapy. Examination revealed aortic systolic and diastolic murmurs, dilatation of the ascending aorta evident on percussion and confirmed by orthodiagram. He was given a total of 2.4 million units of penicillin starting with 5,000 units every 3 hours and reaching a maximum dosage of 40,000 units every 3 hours after 36 hours. The pre-penicillin electrocardiogram was normal. There were no untoward reactions to treatment. He was re-treated 6 months later and this time received 2.4 million units of penicillin starting with the maximum dose of 40,000 units every 3 hours. An electrocardiogram made the day treatment was begun, showed slight T wave changes. On the second day the electrocardiogram showed inversion of T_2 and T_3 and slurring of the QRS complexes; by the fifth day the inversion was only slight; and on the last day the electrocardiogram was normal. Electrocardiograms

4½ and 6½ months later were also normal.

Comment. In no instance did we find it necessary completely to interrupt treatment because of untoward reactions. One patient who had an aneurysm and aortic regurgitation suffered an attack of cardiac asthma during treatment, but he had experienced similar attacks before penicillin. Another patient with aortic aneurysm developed slight precordial constriction on the third day of treatment, but the symptoms were not entirely typical of angina pectoris.

The lack of untoward symptoms in patients with severe myocardial lesions is most noteworthy. Two patients with probable ancient posterior infarctions experienced no untoward reaction to penicillin therapy. Five patients with aortic regurgitation and one with aortic regurgitation and aneurysm who were in marked cardiac failure were treated with penicillin at the same time measures were taken to combat congestive failure; not only did they tolerate both treatments very well, but all were markedly improved on discharge. This is contrary to the accepted belief that patients with cardiovascular syphilis in cardiac failure do not tolerate potent spirocheticidal drugs.

In the pre-penicillin era both cardiologists and syphilologists were of the opinion that antisyphilitic treatment should be postponed in cases of congestive failure until compensation was restored. Although this is too small a group on which to base definite conclusions, our observations suggest that congestive failure in syphilitic heart disease may not be a contraindication to immediate penicillin therapy.

No clear-cut case of therapeutic paradox was observed in this series of patients. As stated previously, the fear of this phenomenon has influenced clinicians to treat cardiovascular syphilis very cautiously. In the era of metal chemotherapy full doses of arsenicals were often never given. One might raise the question whether this did not result in too little treatment. It is most difficult to evaluate symptoms in a condition where the pathologic changes are such that untoward symptoms are prone to occur with or without treatment. Arteriosclerosis is not infrequent in individuals with syphilitic aortitis. It is conceivable that coronary occlusion occurring during the course of antisyphilitic treatment is not due to the so-called therapeutic paradox, but sclerotic coronary vessel or ostium. to the coincident closure of an arterio- Sudden death in syphilitic aortitis and spontaneous rupture of an aneurysm cannot be considered unusual with or without treatment. Therefore, the appearance of severe symptoms during treatment does not *per se* indict the treatment as the cause.

It is well known that T wave changes may be due to numerous factors other than heart disease, but to the best of our knowledge, with the exception of digitalis in the decompensated cases, such factors were not operative during this study. The effects of digitalis were considered in the interpretation of the electrocardiograms. T wave and RS-T segment changes may occur in a small percentage of normal young individuals. In 3107 such cases[4,5,14] only 15 (0.5%) showed T wave changes in Lead II, and in none was the T wave in Lead I inverted. In Wood, Wolferth and Miller's[14] studies of an older age group inverted T waves in Leads I and II were associated with cardiovascular disease in all cases followed. In our group of 50 patients only 7 (14%) were under the age of forty.

Although a fairly large percentage (30%) of our cases showed electrocardiographic abnormalities either before, during, or after treatment with penicillin, one cannot conclude that they were all directly or solely due to

the syphilitic infection. Arteriosclerosis undoubtedly was present in many patients in the upper age groups, and in others, especially those with aortic regurgitation, the ECG abnormalities were in part at least of the type seen in left ventricular hypertrophy. Conversely, the changes in the T waves which occurred as the result of treatment with penicillin cannot be construed as being due to alterations in the arteriosclerotic state or the left ventricular hypertrophy due to damaged aortic valves. Webster and Reader[13] demonstrated at autopsy, active inflammation in the aortas of inadequately treated patients with syphilitic aortitis. Hu, Lin, Chen, and Frazier[6] reported the isolation of virulent Treponema pallidum from the aortas of patients, dying from cardiovascular syphilis, 32 hours after death. In view of these findings, one may speculate that changes within actively involved tissue about the orifices of the coronary vessels may be responsible for electrocardiographic abnormalities during and following treatment with such a potent spirocheticidal agent as penicillin. Because of the great differences of opinion among pathologists[1] as to the interpretation of myocardial scars and small cellular foci found at postmortem examination of patients with cardiovascular syphilis, it is impossible to form an opinion as to whether any of the abnormalities are due to syphilitic involvement of the myocardium. The possibility that there may be changes in chemical constituents of the blood during penicillin therapy which may cause T wave changes must also be considered, although we are not aware of any studies on this subject.

There are clear indications that penicillin is of value in the treatment of syphilitic heart disease, especially in patients where the pathologic process is not far advanced. However, it would be unwise to draw too sweeping or definite conclusions concerning individual items of beneficial effect at this writing. Prolonged observation of a larger group of cases is needed. The fact that the course of syphilitic heart disease is variable and often unpredictable was borne out in a recent report by Reader and his associates.[9]

We are continuing to re-examine the patients at intervals and intend to report their status at some future date.

Summary. 1. Fifty patients with cardiovascular syphilis were treated with sodium penicillin in aqueous solution in total dosages ranging from 1.2 to 9.6 million Oxford units. Only 4 patients in the series had received metal chemotherapy within a 3 month period prior to penicillin. There were 23 diagnosed uncomplicated aortitis, 20 with aortic insufficiency, 5 with aortic aneurysms, and 2 with both aneurysms and aortic insufficiency.

2. There appeared to be no relationship between the amount of penicillin in the initial dose and the occurrence of a febrile Herxheimer reaction.

3. More than half of the patients[28] had electrocardiograms at approximately 3 day intervals during the course of treatment. Electrocardiographic changes (significant T wave changes) were noted during the course of treatment in 8 patients.

4. In no instance was it deemed necessary to discontinue penicillin because of untoward reactions.

5. The 6 patients who were in congestive failure were able to tolerate penicillin simultaneously with the measures for counteracting cardiac decompensation. Thus, contrary to the heretofore accepted practice of giving no potent spirocheticidal drug to decompensated cardiovascular syphilis patients, it does not seem necessary to delay penicillin treatment until compensation is restored.

6. There has been no unequivocal instance of "therapeutic paradox" in

this series during the period of observation, though sufficient time has not yet elapsed to warrant drawing definite conclusions.

7. The material thus far studied indicates that penicillin is a valuable agent in the treatment of syphilitic heart disease.

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THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS
A Report of 24 Cases Treated with Penicillin

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The therapy of subacute bacterial endocarditis has always presented a challenge to the physician, and it is only since the introduction of penicillin that anything approaching encouraging mortality statistics has been achieved. In Table 1 the relative effectiveness of the various therapeutic methods that preceded the antibiotics is compared with penicillin.

TABLE 1.—RESULTS OF DRUG THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

Method	Recoveries
Spontaneous	1- 3 %[6]
Sulfonamides	0- 3.4%[6,11]
Sulfonamides plus Fever	12.1%[3]
Sulfonamides plus Heparin	23.3%[3]
Massive I. V. Sulfadiazine	37.5%[11]
Penicillin	70-80 %

Although the sulfonamides appreciably raised the incidence of cures, their use entailed a high treatment fatality risk. Schein and Baehr,[11] in their report of sulfadiazine therapy, listed a 6% mortality due to treatment. The use of heparin, thought to be warranted by some investigators as an adjunct to the sulfonamides by allowing increased penetration of the fibrin clot, is in itself not without danger from hemorrhagic complications.

Twenty-four cases of subacute bacterial endocarditis (including 2 of subacute bacterial endarteritis) have been treated with penicillin at the Henry Ford Hospital since 1944. Due to the scarcity of the drug during the early period, several of these cannot be thought to have been treated adequately by present standards. A review of the literature on penicillin treatment in various clinics reveals considerable variation in daily dosage, method of administration, and duration of therapy. Only after a larger number of penicillin-treated cases have been reported and analyzed, can criteria for effective management be established.

Age, Sex, and Cardiac Lesion. Twelve of our cases were males and 11 were females. The distribution throughout the various age groupings is found in Table 2. Three cases under 20 years of age had congenital cardiac lesions, 2 having patent ductus arteriosus with superimposed infection and the third a patent interventricular septum. The remaining 20 cases were of rheumatic etiology; 13 involving the mitral valve alone, 2 the aortic valve alone, and 5 combined involvement of both mitral and aortic valves.

TABLE 2.—AGE DISTRIBUTION

Age Grouping	No. of Cases
10-19	4
20-29	3
30-39	6
40-49	7
50-59	2
Over 60	1

At autopsy one case (No. 20, Table 8) was found to have a bicuspid aortic valve, but this was taken to be due to erosion and secondary separation of the valve attachments from the commissures rather than a congenital defect. Three of our cases manifested auricular fibrillation at the time of diagnosis (incidence of 12.5%).

Table 3 shows the length of time that symptoms had been present before

a definite diagnosis of subacute bacterial endocarditis was made. Because of its insidious onset and protean character, the disease frequently remains unrecognized for long periods and is often misdiagnosed during the early stages. The frequency of presenting symptoms corresponded, in the main, with a previous series reported from this hospital and with those from other clinics.[6,12]

TABLE 3.—DURATION OF SYMPTOMS PRIOR TO DIAGNOSIS

Time	No. of Cases
Less than 3 weeks	3
3 weeks to 3 months	9
4 months to 6 months	6
7 months to 1 year	6

Organisms and Sensitivity. (See Table 4). In 2 of our cases, both aerobic and anerobic blood cultures were repeatedly negative. In both instances the history, clinical findings, and subsequent course confirmed the diagnosis beyond a reasonable doubt. Unfortunately, arterial punctures were not done; possibly they would have yielded the desired information.

Sensitivity to penicillin *in vitro* was determined in all but 6 cases. Of the more highly sensitive group (.005 units per cc. to .05 units per cc.) involving 15 cases, there was only one death, showing that there tends to be a practical relationship between organism sensitivity and therapeutic results. In one case (No. 20, see Table 8) the organism was not inhibited by 50 units per cc. of penicillin but was inhibited by 20 units per cc. of streptomycin.

Dosage, Duration of Therapy, and Mode of Administration. The total dosage of penicillin varied from 1,800,000 units to 194,000,000 units (average, 26,900,000 units). The average daily dose was 800,000 units. Duration of therapy varied from 16 to 97 days (average, 34.5 days). The wide variation in dosage and length of treatment was influenced partly by the response to therapy in each case and partly by the scarcity of penicillin during the early part of the series.

Various routes of administration, with the exception of the oral, were used (see Table 5), and in many instances 2 or more routes were tried in the same patient. In many cases the continuous intravenous method was employed initially, to be replaced later by the intermittent intramuscular route due to the development of thrombophlebitis at the site of injection, despite the use of small amounts of heparin in the vehicle.

TABLE 4.—BACTERIA FOUND AND THEIR SENSITIVITY TO PENICILLIN

Organism	Cases	Sensitivity to Penicillin Units/cc.	Cases
Neg. culture	2		2
Strep. viridans	18	.005	7
		.05	4
		.25	1
		Not inhibited by 50	1
		Not done	5
Non-hemolytic strep.	2	.005	2
Staph. aureus	1	.05	1
Hemolytic Staph. albus	1	Not done	1

Results. Of the 23 patients, 5 are dead; the 18 alive are free from evidence of infection with subsequent periods of observation varying from 5 months to 4 years.

A patient was regarded as having relapsed when he was found to show

TABLE 5.–MODE OF ADMINISTRATION

Route	No. of Cases
Continuous Intravenous	8
Intermittent Intramuscular	4
Contin. Intrav. + Intermittent Intramusc.	10
Contin. Intravenous + Contin. Intramusc.	1
Intermit. Intramusc. + Penic. in Wax	1

TABLE 6.–DURATION OF CLINICAL OBSERVATION FOLLOWING CESSATION OF THERAPY

Length of Observation	No. of Cases
Less than 6 months	1
6 to 12 months	7
1 to 2 years	5
2 to 3 years	3
3 to 4 years	3

evidence of recurrent infection including a positive blood culture at any time within 1 year from the date of the cessation of treatment.[3] This occurred in 6 of our cases (as shown in Table 7) with eventual death in 4. One patient (Cases 16 and 17, see Table 8) had a re-infection 14 months following his first episode. On both occasions the organism was streptococcus viridans, but unfortunately no tests for penicillin sensitivity were made. Each time the clinical response to the drug was satisfactory. In the interval between infections the patient had an episode of fever and joint distress with negative blood cultures that responded promptly to the administration of salicylates and was considered to be acute rheumatic fever.

Deaths. Death occurred in 5 of our patients, 4 of whom had suffered one or more clinical relapses as shown above (Table 7). In 3 cases death was directly attributable to cardiac failure (Cases 6, 8, 20, see Table 8) and in one to infection plus cardiac failure (Case 5). In the remaining fatality (Case 7) death followed a subarachnoid hemorrhage.

Other Therapeutic Measures. Sulfonamides were employed in varying dosage in 8 cases. From a review of the case records the indications for the addition of this medication were not always obvious. In some of these cases the drug was not administered in adequate therapeutic dosage and its effectiveness was always difficult to evaluate.

In the 2 cases of bacterial endarteritis a patent ductus arteriosus was successfully ligated during the course of penicillin therapy.

Because of the extreme resistance of the organism *(Strep. viridans)* to penicillin in Case 20 (Table 8), streptomycin was administered in a dosage of

TABLE 7.–RELAPSES

Case No.	No. Relapses	Months Duration of Disease	Organism	Total Dosage Units in millions	Route†	End Result
7	5	12	strep. viridans	194.	CIV-IM	Dead. Subarachnoid Hemorrhage
6	2	1½	strep. viridans	1.8	CIV-IM	Dead. Cardiac failure
20	1	7	strep. viridans	9.*	CIV-IM	Dead. Cardiac failure
8	1	17	strep. viridans	36.	CIV	Dead. Cardiac failure
21	1	8	non-hem. strep.	9.	CIV	Well. 36 months
23	1	3	strep. viridans	16.	IM	Well. 13 months

† CIV–Continuous intravenous.
IM–Intramuscular.
* Also received 96 gm. streptomycin.

TABLE 8.--DATA ON 24 CASES OF SUBACUTE BACTERIAL ENDOCARDITIS TREATED WITH PENICILLIN

Case No.	Age	Sex	Heart Lesion	Duration of Symptoms	Organism	Sensitivity (units/cc)	Daily † Dosage (units in thousands)	Duration of Therapy (days)	Total Penicillin (units in millions)	Duration of Observation (months)	Sulfa	Recurrences	Deaths
1	40	F	RHD MS MI Aur. Fib.	5 mos.	Strep. viridans	0.005	CIV 200	21	4.2	47			
2	17	F	Patent Ductus	5 mos.	Hemolytic Staph. albus	-	CIV - IM 100	18	1.8 Surg. ligation	46			
3	35	F	RHD MI	3 wks.	Strep. viridans	0.05	CIV 200	21	4.2	33	78 gm		
4	16	M	RHD MI	1 wk.	Strep. viridans	0.005	CIV 200	21	4.2	11			
5	35	F	RHD MI	5 mos.	Strep. viridans	0.005	CIV - IM 200	18	3.6		60 gm		Infection Failure
6	49	M	RHD MS MI AI	4 wks.	Strep. viridans	0.25	CIV - IM 200	9	1.8		88 gm	2	Cardiac Failure
7	44	M	RHD MS MI	4 mos.	Strep. viridans	-	CIV - IM 80 2000	7 90	194.0			5	Subarac Hemorr.
8	20	M	RHD MS MI AS AI	1 yr.	Strep. viridans	-	CIV 200 400 600 1000	21 6 24 12	36.0	5		1	Cardiac Failure
9	49	F	RHD MI	10 mos.	Strep. viridans	0.005	CIV - IM 500	30	15.0	25	22 gm		
10	41	F	RHD MI	6 mos.	Strep. viridans	0.05	CIV - IM 200 1000	16	14.4	13			
11	22	M	RHD MS MI AI	7 mos.	Strep. viridans	0.005	CIV - IM 400	38	11.6 add. amts. at home	7			
12	14	F	RHD MS MI AS AI	6 wks.	Strep. viridans	0.005	CIV - IM 200	33	6.6	9			
13	48	M	RHD AS AI MI	7 wks.	Strep. viridans	0.05	CIV 200 400	19	6.0	22			
14	10	M	Patent IV Septum	12 mos.	Culture neg.	-	IM 400 800	50	38.4	7			

13	48	M	AS AI MI	[illegible] wks.	viridans	[illegible]	[illegible] 400	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
14	10	M	Patent IV Septum	12 mos.	Culture neg.	-	IM 400 800	50	38.4	7			
15	38	F	RHD MS MI	5 mos.	Staph. Aureus	0.05	IM 800 2400	38	68.8	7			
16	36	M	RHD MS MI Aur. Fib.	10 wks.	Strep. viridans	-	CIV 200 400	22	7.6	14			
17	Same as patient # 16			6 wks.	Strep. viridans	-	IM 800 1000 2000	40	48.0	11			
18	55	F	RHD MS	7 mos.	Strep. viridans	0.005	CIV - IM 800 1000	36	31.2	15			
19	33	F	RHD MS	10 days	neg. culture	-	IM 300 in oil 400 1000 2000	52	71.5	8	25 gm		
20	34	M	RHD AI Bicuspid aortic v.	10 wks	Strep. viridans	not inhib. 50.	CIV 600 8800 1000	13	9.8	3½	89 gm	1	Cardiac Failure
						20.0 Streptom.	1 gm 2 gm	48	96 gms.				
21	65	M	RHD MI	7 mos.	Non-hemolytic Strep.	0.005	CIV 200 400	36	9.0	38	*	1	
22	45	M	RHD MS MI Aur. Fib.	10 days	Strep. viridans	0.05	CIV - CIM 400 400	29	11.6	27			
23	58	M	RHD MI	6 wks.	Strep. viridans	-	IM 200 400 800	18	16.6	16	19 gm	1	
							200 320 400	24					
24	23	F	Patent Ductus	6 wks.	Non-hemolytic Strep.	0.005	CIV 400 500 1000	22	13.8	5			

* Received prior to admission.
† CIV - Continuous intravenous.
IM - Intramuscular.
CIM - Continuous intramuscular.

2 gm. daily for 48 days. Vestibular manifestations consisting of dizziness and nystagmus began soon after starting treatment and persisted until death from congestive heart failure. Clinical arrest of the infection was apparently accomplished, although 1 positive blood culture was obtained 2 months prior to death.

Discussion. Although it is important to establish a standard plan for the treatment of subacute bacterial endocarditis, it is necessary that the physician be ready to regulate the therapy to suit the requirements of the individual patient. Factors to be taken into consideration include the duration of the disease at the time the diagnosis is made, clinical condition of the patient, nature of the offending organism and its response to penicillin *in vitro*, record of any previous therapy, and the symptomatic and clinical response of the patient after treatment is under way.

The supportive measures are those necessary in any long continued infectious process. Diet should be high in calories and easily tolerated. A low sodium intake is indicated in view of the significant incidence of congestive failure. Transfusions are usually unnecessary but should be used without hesitation if one is faced with a dangerously low or falling hemoglobin value during therapy. Digitalis is indicated only if congestive failure develops. Oral iron preparations are useful to combat the secondary anemia, and high potency multivitamin mixtures may be desirable in general supportive care. Strict confinement to bed is not necessary or advisable in the absence of symptoms or signs suggestive of the onset of congestive heart failure.

Penicillin is the specific therapeutic agent of choice in the majority of cases. The various better known fractions (F, G, K and X) have not as yet been evaluated sufficiently to know which is most effective.[2] Streptomycin should be employed in those cases involving gram negative organisms or where penicillin resistance has been demonstrated by *in vitro* laboratory tests. Anticoagulants as an adjunct to aid in the penetration of the valvular vegetations by the antibiotics seem superfluous and not without danger, although Loewe still advocates the use of heparin.[7] Sulfonamides have proved to be far inferior to penicillin (Table 1) and at present are to be considered only after adequate penicillin and, or, streptomycin therapy have failed.

A survey of the current literature reveals no unity of opinion regarding the daily dosage of penicillin, the duration of therapy, and the optimum route of administration.

Various clinics have recommended daily doses of penicillin varying from 200,000 to 1,200,000 units in the average case, and it would appear that, with this passage of time, the figures are being revised upward[1,5,7,9,10,13]. Theoretically, the sensitivity of the offending organism to penicillin should give us at least the starting point for estimating an adequate dose. If the causative organism is inhibited by 0.05 units or less of penicillin per cc. of culture media, one may expect therapeutic success with moderate daily doses. Tumulty and Harvey,[13] however, emphasize that many organisms appearing resistant will respond to an average dose. It is also true that some organisms which appear sensitive to *in vitro* tests will not respond to the corresponding dose of the drug. In general, it seems advisable to administer the drug in doses which will give a blood level 5 to 10 times the minimal amount effective *in vitro*. In the treatment of relapses a substantial increase in both the daily dose and the duration of treatment should be made regardless of the *in vitro* sensitivity of the organism.

The clinical response of the patient to a given dosage schedule will regulate the subsequent schedule. Within the first few days the patient should show clinical signs of improvement. The persistence of occasional embolic episodes early in the course of treatment need not be construed as an indication of therapeutic failure.

Loewe[7,8] and also Christie[1] have utilized both intravenous and intramuscular routes of administration with success. Flippin and his associates[2] preferred the intermittent intramuscular technique with "booster" injections periodically in resistant cases. More recent reports[10,13] suggest use of the intermittent intramuscular route for average doses and utilization of the continuous intravenous method only if the daily dose is to be 3,000,000 units or greater. The final choice of route should be determined by the ease of administration and comfort of the patient in the cases calling for moderate doses of the drug. If the continuous intravenous route is used, 5% glucose in water as a vehicle rather than normal saline should be employed due to the undesirable amount of sodium introduced by the former method. The frequent occurrence of thrombophlebitis at the site of administration and the inconvenience to the patient incurred by this method leads us to favor the intermittent intramuscular route. We have occasionally employed the "booster" doses as advocated by Flippin and have found them to be advantageous.

Loewe[8] estimates that with the continuous intravenous method a blood level of approximately 1 unit per cc. may be obtained for each 1,000,000 units of the drug given daily. This determination may be used as an initial guide in estimating the dosage based on *in vitro* sensitivity of the organism. Although significant elevations of the blood level of penicillin have been reported by the concurrent use of various compounds such as para-amino-hippuric acid and caronamide, our experience along this line has been limited. Certainly the use of these compounds seems to offer promise in selected cases.

Tumulty and Harvey[13] point out that the goal of any therapeutic regimen is the cure of the maximum number of patients and not the determination of the smallest amount of a therapeutic agent which will be effective in the majority of patients. For this reason, it does not seem extravagant to overtreat some patients in order to secure adequate treatment of all. The authors mentioned above cite 4 cases with apparent clinical arrest of the infection who died from other causes and at autopsy still showed evidence of active endocarditis. Christie[1] emphasizes the duration of the treatment, irrespective of the total dosage, as an important factor.

At the present time there is no general agreement as to the criteria for adequate treatment. Priest *et al.*[9] state: "The only consistently reliable guides after cultures of the blood have become sterile are the leukocyte count and the blood sedimentation rate." Tumulty and Harvey,[13] on the other hand, believed that the best indications of effective therapy were the return of the temperature and pulse to normal, a gain in weight, the absence of sweats, an increasing sense of well being of the patient, the subsidence of embolic phenomona, and the elevation of the red count and hemoglobin toward normal. We believe that the clinical response of the patient is a more reliable index to adequate therapy than laboratory determinations. Duration of therapy based upon the above standards will vary in individual cases, but 5 weeks should probably be regarded as a minimum for continuous therapy in uncomplicated cases.

Relapses usually occur within 3 or 4 weeks after cessation of therapy and,

in our experience, are usually of serious prognostic import (see Table 7). Therapy should be resumed, a more intensive program used, and streptomycin administered where indicated as previously outlined. The largest total dosage in our series was 194,000,000 units, although a case has been reported which was given a total of 1,450,000,000 units with recovery.[13]

Considerable difference of opinion exists as to whether cardiac failure is hastened due to further scarring of the valves during the healing process. It must be conceded, however, that successful therapy for subacute bacterial endocarditis by increasing longevity of this group of patients will magnify the importance of congestive failure as a cause of death in rheumatic heart disease.

As pointed out above, the occurrence of embolic episodes during the course of treatment is not necessarily evidence of inadequate therapy, although its frequent occurrence probably indicates the need for prolongation of the course of the drug.

The occurrence of thrombophlebitis at the site of continuous intravenous injections has already been discussed, and we have not encountered necrosis of muscle secondary to intermittent intramuscular administration.

The use of penicillin prior to and following dental extractions and tonsillectomy in patients with valvular heart disease is definitely warranted. Recent work suggests that an effective penicillin level should be continued for at least 48 hours post operatively.[4] Foci of infection should be diligently searched for in all patients undergoing therapy for subacute bacterial endocarditis and, if possible, should be eliminated during the course of penicillin treatment.

The final determinants of success in the therapy of this disease with penicillin are not primarily such factors as age, duration of the disease, or the valves involved, but rather the degree of cardiac disability, the critical nature of the embolic phenomena and the resistance of the offending organism.[13]

Our mortality rate of 21.7% compares favorably with 374 cases collected from the recent literature whose overall death rate was 26.6%.[1,5,7,9,10,13] It is to be expected that refinements in antibiotic therapy in the future will significantly improve upon this figure by eliminating failures due to recurrent infection.

Summary. A total of 24 cases of subacute bacterial endocarditis treated with penicillin involving 23 patients is reported in detail. Eighteen are living and free from evidence of infection 5 months to 4 years following cessation of treatment.

A correlation between sensitivity of the organism *in vitro* and the *in vivo* response to antibiotic therapy is demonstrated. The importance of clinical relapse as an unfavorable prognostic sign is pointed out.

Factors to be considered in setting up a rational program of therapy are discussed. The importance of congestive heart failure as a complication is stressed and suggestions for its prevention are outlined.

Streptomycin is advocated for those cases in which a marked *in vitro* resistance or a lack of clinical response to massive doses of penicillin is encountered.

An overall mortality of 21.7% for this series compares favorably with other series previously reported.

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MODIFICATION OF THE CARDIAC OUTPUT AFTER INTRAVENOUS INJECTION OF HYPERTONIC GLUCOSE SOLUTION

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GLUCOSE is known as one of the most important nutritive substances for muscular tissue, and its stimulating action on the heart in the heart-lung preparation has been shown by Bayliss, Muller and Starling[1]. Glucose therefore, has been recommended in the treatment of patients with cardiac disease and is usually used intravenously in hypertonic solutions at a concentration from 20% to 50%[9,10]. However, quantitative determinations of the effect of glucose on the work of the human heart, to our knowledge, have not yet been reported. The present study has been performed in order to measure the modification of the cardiac output induced by hypertonic glucose solution. The determinations of cardiac output have been made by the ballistocardiographic method of Starr[12]. The effect of the injection has been studied in normal subjects and in patients with cardiovascular disease.

Technique. The subjects were studied at least 2 hours after a meal and a control ballistocardiographic record was taken after 15 minutes rest. Then they received an injection of 50 cc. of a warm glucose solution at a concentration of 50%; the injection was always made intravenously in 20 to 40 seconds. A series of ballistocardiographic records were taken successively at 1, 2, 3, 4, 5, 6, 8, 10, 15, 20 and in a few cases up to 45 and 60 minutes. The results are calculated in percentage of minute output modification of the control record. Only increases of 10% or more above the control record were regarded as significant.[14]

Blood pressure was estimated at intervals by the sphygmomanometer in some, but not all of our subjects. No significant changes were found after the injection and, as we preferred not to disturb the subjects in any way, we omitted these estimations in the last part of the study.

These determinations have been made in 9 subjects with normal hearts, and in 14 patients with evidence of heart disease (2 with questionable heart disease, 2 with arteriosclerotic heart disease, 3 with congestive failure of variable etiology, 6 with hypertension and 1 with nephrosis). All of the patients with cardiac disease were ambulatory at the time of the test and all were capable of reclining on the ballistocardiographic table without severe orthopnea.

The results were subjected to a statistical analysis by the methods of Fisher[5] and the word "significant" is used in the statistical sense, indicating a probability of less than 5 in 100 that the difference was due to chance.

Results. The data are given in Table 1. In normal subjects, the hypertonic glucose solution induced an augmentation of the cardiac output lasting about 5 minutes after the injection. The maximum augmentation reached 10% to 30%. After 5 to 8 minutes, the cardiac output reached its normal level, and in many cases dropped thereafter to a lower level.

A strikingly different response was obtained in the great majority of our patients with cardiovascular disease. The augmentation of the cardiac out-

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put lasted much longer than in normal cases and was generally still present 15 or 20 minutes after the injection. In some subjects, however, we observed a transient drop of the cardiac output during the first minutes following the injection and a later increase.

In making the statistical analysis it seemed best to exclude the patients with questionable cardiac disease (Patients 10 and 16) even though their inclusion would have made no material difference.

The average duration of the increased cardiac output in patients with cardiac disease is very significantly longer than in the normal group; indeed there is no overlapping of the two groups. The difference between the maximal increase of cardiac output, expressed as percent of the control value, is significant but less striking. The mean maximal increase is 35.9% in the cardiac group and 19.3% in the normal group. In 3 cardiac patients (Patients 18, 19 and 23) the maximal increase in cardiac output was 50% or more; these increases stand out from the other data. If these 3 results are excluded from the cardiac group, its mean increase becomes 25.2% instead of 35.9% and statistical analysis reveals that this value is not significantly different from the normal average.

The modifications in cardiac output were not correlated with any significant change in heart rate, indeed the rate changed but little in most experiments. However, in 1 normal subject (Patient 8 in the Table) a transient slowing of the heart beat occurred from the first until the second minute after injection.

Discussion. As successive estimations of cardiac output by the ballistocardiogram agree within 10% (the standard error of estimation of the second from the first is 4.8% of the second value[14]), our results show that hypertonic glucose solution induces an augmentation of the cardiac output both in normal subjects and in those with cardiac disease. As the blood pressure did not change significantly in the subjects studied, the work of the heart must have increased. In normal subjects this augmentation was transient; in cardiac disease it was much more prolonged.

Glucose, therefore, is another example of the group of physiological agents which affects the cardiovascular systems in disease in a manner different from the effect produced in healthy persons. This is also true of such familiar agents as digitalis[2,13,11] and theophylline ethylene diamine[6] injected intravenously; and doubtless of many other agents. And it is of no little interest that all three of the agents mentioned above cause a stimulation of the circulation more pronounced and enduring in disease than in health.

The action of hypertonic glucose that we have demonstrated might have been brought about by the glucose itself, by the hypertonicity of the injected solution, or by both means. In normal subjects the augmentation of the circulation was transient. A similar effect has been observed after the injection of hypertonic saline solution[7] and this raised the question whether the response is due to their common property, hypertonicity, rather than to a specific effect on the heart. It is known that hypertonic solutions attract a certain amount of water from the tissues into the blood, increasing the blood volume and the venous pressure[4]. Whether this latter fact could explain the initial augmentation of the cardiac output, in accordance with Starling's Law of the Heart, was investigated and the results are recorded in the following paper.

On the other hand, the long lasting augmentation of the output observed in cardiac patients might be due to a beneficial action of glucose on the heart. It should be recalled that in

TABLE I. -- CHANGES IN CARDIAC OUTPUT AFTER INTRAVENOUS INJECTION OF 50 CC. OF 50% GLUCOSE

Name	Diagnoses	Remarks	Minutes After Injection												
			1	2	3	4	5	6	8	10	15	20	30	45	60
1. JF	Normal		+12	+ 8	+ 8	+ 1	- 4	- 8	- 4	- 4	- 9	- 7			
2. JS	Normal		+17	+15	+20	+20	+ 6	- 1	+ 1	- 1	- 3	+ 1			
3. BC	Normal		+26	+17	+ 2	+ 1	0	- 4	- 8	-15	-10				
4. BB	Normal		+12	+22	+29	+ 4	+10	0	- 4	- 9	- 7				
5. GZ	Normal		+ 4	+ 6	+ 6	+ 1	+ 1	0	-12	-12	-17	-20			
6. HS	Normal		+ 6	+13	+ 2	+ 1	- 5	0	0	0	0				
7. HW	Normal			+ 8			- 1			-11	-11	-15	-15		
8. JW	Normal	With transient slowing of heart rate	+30	-10	0	+ 4	0	0	+ 7	+ 5	0	0			
9. SS	Normal		+14	+23	+30	+ 4	+10	0	- 5	- 8	- 7				
10. CD	Normal?	Periph. artscl., ECG early L.V. hypert. Class E	+24	+10	+10	+17	+17	+15	0	- 7	- 5	- 7			
11. HS	Artscl. Ht.Dis.	Angina of effort, dysp. at rest, mild cong. failure, ECG L.V. hyper., old infarct, ant. wall, Class III D	+28						+23	+13	+18	+23			
12. JK	Artscl. Ht.Dis.	B.P. 175/110 dysp. on sl. exertion, no angina, ECG: myocard. dam., ht. enl. Class III C			+14							+16			
13. VC	Cong. Failure	Mod. Hypertension, recov. from pul. edema and severe failure, advanced renal dis., digitalized. Class III D	+13	+14	+ 8		+ 8			+20	- 1	+10	0	0	
14. AG	Cong. Failure	Chronic Pul. dis., marked dysp., digitalized. Class IV D		+32					+32		+26		+36	+33	+37
15. RA	Cong. Failure	Marked dysp. on exertion, enl. ht., fever; ECG low voltage QRS, T waves flat, digitalized; liver biopsy showed miliary Tb. Class IV E		+21			+34			+36	+29	+32	+24	+21	
16. DR	Normal?	Meningo-vasc. syph. ECG notched P waves, deep notched T wave Leads II, CR_2 & CR_3. Class E	+ 7	+15	+15	+14	+13	+13	+13	+13	+10	0	-11		
17. DS	Hyper-tension	B.P. 156/108 no dysp. ECG L.V. hyper. and myocard. dam. Class I B	+25						+20		+ 4				
18. LF	Hyper-tension	B.P. 200/100 prog. incr. dysp., renal insuf. ECG L.V. hyper. Class II C	+63	+24	+24	+21	+21	+12	+29	+25	+25	+20			
19. BL	Hyper-tension	B.P. var. 200/100 to 170/80 sl. dysp. on exertion, ht. sl. enl., ECG advanced L.V. hyper. Class II C	+91	+68	+45	+41	+26	+26	+17	0					
20. GD	Hyper-tension	B.P. 230/140 bilat. sympath. 1941, no dysp., mod. card. enl., ECG ad. L.V. hyper. Class II B	- 3	+ 4	+ 4	+14	+14	+14	+14	+14	+ 7	+ 5			
21. DC	Hyper-tension	B.P. 200/125 no dysp. latent syph., ECG L.V. hyper. Class I B	+22	- 1	- 3	- 3	+ 1	+ 2	+ 4	+ 5	+18				
22. LG	Hyper-tension	B.P. 250/190 mod. dysp. on exertion, ECG early L.V. hyper. Class II C	+29	0	+ 5	+ 9	+ 5	+ 5	+ 9	+11	+19	+19			
23. JF	Nephro-sis	Stage of Glomerulonephritis, anasarca, dysp. on exertion anemia, B.P. 150/100. Class III D	+50	+50	+43				+38			+13			

The numbers indicate the percentage of modification in cardiac output above or below its level before the injection

animal preparations, glucose has a more favorable effect on the contractility of a failing heart than of a powerful heart[1,3]. Our results indicate that the same may be true in human beings.

Of those patients with cardiac disease who showed a prolonged increase in cardiac output, there was no apparent common factor except cardiac abnormality. It was our impression that the most striking increases and prolongations of cardiac output were roughly proportional to the degree of dyspnea and perhaps to the degree of cardiac insufficiency, but this relationship is not too clear. Patient 16, aged 17, with meningo-vascular syphilis, had no evidence of cardiac disease except an abnormal electrocardiogram, yet his cardiac output remained elevated for 15 minutes after the glucose injection.

None of the patients with cardiac disease stated that they felt any subjective benefit following the injection, nor were any unfavorable effects noted. Objections have been raised to the therapeutic use of hypertonic glucose solution in patients with coronary insufficiency. It has been reported in these cases to cause a significant alteration of the electrocardiogram; moreover some patients are reported to have complained of severe precordial pain[8]. In our experiments the injection was always performed rapidly, but the only complaint recorded was a warm sensation throughout the body lasting a few seconds. Moreover, the maximal augmentation of the cardiac output immediately after the injection was usually not very great, and the heart was not subjected to a sudden increase in its work. In our one patient with true angina of effort (Patient 11 in the Table) anginal pain was not produced.

Summary and Conclusion. Hypertonic glucose solutions injected intravenously induced an augmentation of the cardiac output as measured by the ballistocardiogram, which generally reached 10% to 30% above the control figure.

Although the average maximal increase was significantly greater in patients with cardiac disease than in healthy persons, the difference was not striking; and, if the data obtained in 3 patients are omitted, the difference is no longer significant.

On the other hand the difference in duration of the effect was very striking and highly significant. The increased cardiac output lasted much longer in patients with cardiac disease.

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23. JF | Nephrosis | Stage of Glomerulonephritis, anasarca, dysp. on exertion | anemia, B.P. 150/100. Class III D
The numbers indicate the percentage of modification in cardiac output above or below its level before the injection

ON THE MECHANISM BY WHICH INTRAVENOUS INJECTIONS OF HYPERTONIC GLUCOSE SOLUTION CAUSE INCREASED CARDIAC OUTPUT

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In the preceding paper[8] it was demonstrated that 50 cc. of 50% glucose solution injected rapidly intravenously was followed by a noteworthy increase in cardiac output which tended to be of longer duration in subjects with heart disease than in healthier subjects. Further studies have been undertaken to answer several questions about the mechanism of this effect.

As was mentioned in the previous paper, two possibilities presented themselves:

1. Hypertonic glucose solution would be expected to draw fluid into the circulation and to increase blood volume, and this might in turn raise the venous pressure and so stimulate the heart according to Starling's Law. According to this concept the increased effectiveness of the glucose in cardiac disease might be attributed to the excess tissue fluid present in such cases as manifest or occult edema. This fluid might be more readily available than the tissue fluids of healthy subjects and so might lead to a more rapid and prolonged increase in blood volume and so to more pronounced cardiac effects.

2. From the results of animal experiments, it was also proper to expect that glucose would stimulate the heart directly. Indeed, the enhanced effect in cardiac disease might be taken to be analogous to the results already obtained in animal preparations[1,2] in which a damaged heart responded more vigorously to glucose than hearts in better condition. This hypothesis is not an alternative to the first and there was no way of testing it directly, but the problem could be approached by excluding other possibilities and finding whether the data were consistent with this concept.

The results demonstrate that, although a significant rise of blood volume did follow the injection of glucose, the increase of venous pressure was so small that it was often negligible and it could not be correlated with the increase in cardiac output. As there is positive correlation between the cardiac output effect and the level of blood sugar after glucose is injected, the data suggest that glucose produces an effect on the circulation directly by cardiac stimuation rather than indirectly by increasing the blood volume.

Subjects. The 22 subjects were all ward patients at the University Hospital and each received a complete hospital study. Four gave abnormal ballistocardiograms and as cardiac output could not be calculated with confidence from such records these data were not used. The patients who had normal ballistocardiograms were divided into 2 groups.

Included in the group with normal hearts was B. M., age 56, with carcinoma of the lung who died 7 weeks after the test and had a normal heart at necropsy. The rest were: T. S. age 54, diagnosed anxiety neurosis; L. B. age 42, with a mild pyrexia of unknown origin; J. Z., age 55, with a mild depressed psychosis; N. V., age 56, who suffered from loss of weight not explained by the study; and H. W., age 26, diagnosed psychoneurosis and primary dysmenorrhea.

Included in the group with abnormal hearts were: O. B., age 40, with luetic aortic valvulitis; L. M., age 29, A. S., age 30, and P. E., age 39, all with rheumatic mitral stenosis; E. M., age 57, with coronary heart disease,

left bundle branch block and angina pectoris; C. W., age 53, who came to the hospital with intermittent substernal pain which later became constant, who showed severe electrocardiographic abnormalities suggesting pericarditis rather than infarction, and who developed azotemia and left the hospital moribund; A. K., age 59, W. H., age 47, G. B.,

TABLE 1.--RELATION OF CHANGE OF CARDIAC OUTPUT PER MINUTE TO CHANGE IN PLASMA VOLUME AFTER INJECTION OF HYPERTONIC GLUCOSE

Subject	Diagnosis	Change in Cardiac Output and Plasma Vol.	Time After Injection at which Samples were Taken and Estimates Made.			
			3 to 8 min.	12 to 18 min.	25 to 30 min.	45 to 50 min.
E.M.	Coronary Ht. Dis.	C.O. per min.%	+ 7	+ 8	- 5	0
		P.V. %	+12	+ 6	+ 4	0
T.S.	Coronary Ht. Dis.	C.O.	+ 3	+ 2	- 5	0
		P.V.	+18	-12	0	
P.E.	R.H.D. Mitral Stenosis	C.O.	+ 4	+20	+10	
		P.V.	+16	+14	+11	
A.S.	R.H.D. Mitral Stenosis	C.O.	+26	+16	+ 6	- 8
		P.V.	+23	+24	+24	+19
L.M.	R.H.D. Mitral Stenosis	C.O.	+17	- 2	- 1	+ 7
		P.V.	+ 4	- 4	- 1	-11
C.W.	Dissic. Aneurism (?)	C.O.	- 3	+12	+ 2	0
		P.V.	+ 5	+ 3	- 3	0
W.H.	Ess. Hypertension	C.O.	+ 5	+ 9	+ 9	+20
		P.V.	+11	+12	+15	+16
L.G.	Ess. Hypertension	C.O.	+12	+ 9	+ 9	+10
		P.V.	+ 9	+ 5	+13	+ 6
A.K.	Ess. Hypertension	C.O.	+ 4	-11	-15	-25
		P.V.	+ 5		+ 2	
B.M.	Normal Heart	C.O.	+12	- 8	- 7	
		P.V.		- 4	- 4	
L.B.	Normal Heart	C.O.	+28	+21	+ 4	+ 3
		P.V.	+16	+16	+10	+19
J.Z.	Normal Heart	C.O.	+ 3	+ 3	- 6	- 4
		P.V.	+12	+ 7	- 1	
N.V.	Normal Heart	C.O.	- 7	- 7	- 4	- 3
		P.V.	+11	+ 9	+14	+ 8
	Average Change in C.O. (%)		+ 9.6	+ 5.5	-.2	0
	Average Change in P.V. (%)		+11.8	+ 6.3	+ 6.5	+ 7.1

age 27, L. G., age 62, O. Y., age 56, and A. M., age 42, had hypertension at or exceeding 180/105 mm. Hg. Of these six, 5 were adjudged to have cardiac abnormality because they had either cardiac enlargement by fluoroscope or a major electrocardiographic abnormality or both. However, C. B., the youngest of them, had no cardiac enlargement and a normal electrocardiogram, but the shape of the heart suggested left ventricular hypertrophy.

All these patients were in good functional condition (Class I) except P. E. who was in mild congestive failure at the time of testing (Class IV); O. Y., admitted in failure, who had recently recovered from it when the tests were made (Class III); and C. W. extremely ill, but with the diagnosis in doubt.

Methods. Plasma volumes were estimated by the dye dilution method using T-1824 according to the technique of Gregerson.[3,4,5] A single sample taken between 10 and 15 minutes after the dye injection was employed to calculate the initial blood volume. Later in the same experiment other blood samples were taken to follow the changing blood volume. The amount of dye in the plasma was estimated from optical density read in a Beckman Spectrophotometer. The changes in blood volume were estimated from the deviation of our samples from the theoretical time-disappearance curve of the injected dye. This curve had been previously determined[5] and I confirmed the findings in 4 subjects.

Hematocrit specimens were centrifuged at a speed of 2500 to 3000 r.p.m. for half an hour.

Venous pressures were taken by the method of Moritz and Tabora, by allowing a saline solution to run into an antecubital vein as far as it would. The needle was left in the vein during the experiment.

Arterial pressures were estimated in the usual manner by the auscultatory method.

Cardiac output was estimated from the ballistocardiograms.[9]

In some experiments blood samples were analysed for sugar and occasionally for chlorides. I am indebted to Dr. J. H. Austin who made these estimates for me.

All patients were tested either fasting or at least 2 hours after a meal kept low in fat content. They lay horizontally on the ballistocardiograph for 15 minutes before the first record was taken. Venipuncture was then performed. Dye was injected, venous and arterial pressures were measured and a ballistocardiogram taken. After these estimations, 50 cc. of 50% glucose was injected in a period of about 30 to 40 seconds. Ballistocardiograms, blood samples and estimations of venous and arterial pressure were taken at intervals for the next 45 minutes or until the effect had died away. Not all the estimations were made on every subject.

Results. *Plasma volume* was estimated repeatedly on 4 of the subjects with normal hearts and on 9 of the group

TABLE II.--RELATION OF CHANGE OF CARDIAC OUTPUT TO CHANGE OF VENOUS PRESSURE AFTER INJECTION OF HYPERTONIC GLUCOSE

Subject	Diagnosis	Change in Cardiac Output and Venous Pressure	Time After Injection at which Samples were Taken				
			2-3 min.	5 min.	8-10 min.	10-15 min.	20-30 min.
O.Y.	Ess. Hypertension	C.O. Per min. %	+ 6	+17	+ 6	+13	+10
		V.P. mm. H_2O	+ 1	- 4	- 3	+ 1	- 4
G.B.	Ess. Hypertension	C.O.	+ 4	- 3	- 1	- 1	- 2
		V.P.	+22	+11	+ 2	- 6	-14
O.B.	Luetic Ht. Disease	C.O.	+20		+16		+12
		V.P.	+12		+16		+12
E.M.	Coronary Ht. Disease	C.O.	+ 6	- 8			- 5
		V.P.	+12				+ 8
L.G.	Hypertension	C.O.	+ 9		+15	+ 9	+10
		V.P.	+13	+ 5	- 1	- 8	- 1
N.V.	Normal Heart	C.O.	+ 8		+ 5	- 7	- 4
		V.P.	+47	+20	+20	- 3	+ 4
H.W.	Normal Heart	C.O.	+ 8	- 1	-11	-11	-15
		V.P.	+32	+30	+22	+17	+15
B.M.	Normal Heart	C.O.		+12		- 8	- 7
		V.P.				+16	+12
	Average Change in C.O. (%)		+ 9	+ 5	+ 5	0	0
	Average Change in V.P. (mm. H_2O)		+29	+12	+ 6.5	+ 3	+ 3

with cardiac disease. The results are given in Table 1. Inspection of the results showed no noteworthy difference between those obtained in the two groups of cases. After the injection of glucose the plasma volume always increased, the average increase for all our subjects being +374 cc. at the end of 5 minutes, +221 cc. between 12 and 18 minutes, +225 cc. between 25 and 30 minutes and +242 cc. in the smaller group tested between 45 and 50 minutes.

Forty-five estimates of cardiac output can be paired with simultaneous estimates of plasma volume. Statistical analysis shows that the correlation between the changes in these 2 values after glucose is significant, the correlation coefficient being 0.41, whereas any value over 0.29 is significant.

Hematocrit values were estimated repeatedly in 21 cases, 5 of whom did not receive glucose. The changes were usually very small; the average packed cell volume diminished 1.6% in 14 samples taken from 2 to 5 minutes after the injection of glucose; 1.9% in 13 samples taken from 10 to 15 minutes; 1.9% in 16 samples taken between 20 and 30 minutes; and 2.1% in 8 samples taken between 35 and 45 minutes. But a tendency towards diminution was also found in those cases not given glucose. Thus 35 to 45 minutes after a dye injection, no glucose being given, the average of 5 samples showed the packed cell volume to have diminished by 0.6%, a value not significantly different from that found after glucose at a similar time. For this reason, as well as the well-known error inherent in calculating the total relation between cells and plasma from blood samples drawn from veins, the results have been reported as plasma volume, rather than as blood volume. The latter was calculated in each case and the data did not change our conclusions.

Venous pressure was estimated repeatedly in 9 subjects of whom 3 had normal hearts and 6 had cardiac disease. The initial pressures were all within normal limits. Results are recorded in Table 2. After glucose there was a slight but definite increase of venous pressure in most subjects. The average increase reached a maximum, 20 mm. H_2O, shortly after the injection, at the time when cardiac output was often at its maximum. This increase of venous pressure was not sustained and in about 10 minutes the average was only 6 mm. above the initial level. From this point the average fell more slowly and was only slightly above the initial level 35 minutes later.

Estimations of the change of venous pressure after glucose can be paired with simultaneous estimations of the change in cardiac output in 30 instances. No relation could be demonstrated as the correlation coefficient, 0.165 was not significant.

Arterial pressure was estimated repeatedly in 6 cases. No important changes were found after the injection in any case tested. A similar result having been secured in the preceding study these estimations were not continued.

Blood sugar was estimated repeatedly in 3 cases. As was to be expected from the many results secured by those interested in the Intravenous Glucose Tolerance Test,[6] a marked increase was found after the injection and the blood sugar remained abnormally elevated during the whole experiment. Table 3 gives these results. The correlation coefficient between blood sugar level and the cardiac output is 0.57, and any value over 0.51 is significant. The blood chlorides did not change significantly.

Discussion. The additional experience gained permits a more exact statement of the relation of the response to glucose and the clinical state of the patients. In this study the patients with cardiac abnormalities used

were not as sick as those tested previously[8] and it is interesting that their cardiac outputs did not increase so much, nor was the increase so prolonged as in the group studied before[8].

The patients with abnormal hearts had been classified according to the functional classification of the American Heart Association before the results of the study were known, and it is of interest to compare this clinical estimate of cardiac capacity with our findings, using the data of both this and the preceding paper[8]. In so doing it seemed proper to omit case L.B. who had a fever of unknown origin and whose cardiac response to the glucose was much more vigorous and prolonged than that of any other person with a normal heart. No other patient was febrile. C.W. was also omitted because the primary diagnosis was in doubt, he was very sick and his cardiac status was hard to assess.

As the difference between the glucose effect on the cardiac and noncardiac groups was most conspicuous late in the test, and as the exact times at which ballistocardiograms were taken varied somewhat, we studied values for cardiac output estimated from ballistocardiograms taken between 15 and 30 minutes after the injection of glucose and, if there was more than one estimate in this period, the average was used. The results were striking. In 14 patients with hearts judged to be normal the average cardiac output per minute at this time was 7% *below* the level found before injection. On 14 patients judged to have cardiac disease but without undue dyspnea on exertion (Class 1) the average was 2% *above* the initial value at this time; in the 3 judged to belong to Class II the average was +16%; in the 5 in Class III, +12%; in the 2 unable to take any exercise without discomfort (Class IV) it was +22%. The numbers in the Classes II, III, IV are too small to warrant statistical analysis of the data from each group separately, so they were combined. The mean obtained in the group with normal hearts is significantly different from that of the Class I group, t being over 3. Similarly the mean of the Class I group is significantly different from that of the combined groups, t being again over 3. Evidently the duration of the response to glucose increases as the functional capacity of the patient diminishes.

The results also throw light on the mechanism by which glucose produces its effect on the circulation. It is true that there is a significant correlation between the increase of blood volume that occurs after glucose and the increase of cardiac output; a similar significant correlation, of about the same magnitude, was found between changes of cardiac output and blood volume in cases subjected to operation[7], but it does not necessarily follow that the one causes the other; in this instance it is more likely that the glucose is the single cause of the two effects. We know of no means by which increased blood volume could stimulate cardiac output except by raising the filling pressure of the heart; and the increase of peripheral venous pressure after glucose was negligible in most cases. Therefore, the increased blood volume could hardly have produced the striking cardiac effects observed. It is true that the greatest average height of venous pressure and the maximum average stimulation of cardiac output in the same subjects coincided at about 4 minutes after the injection, but the change in peripheral venous pressure was always very small, averaging only 2 cm. at this time. Warren *et al.*[10] have presented evidence that changes in cardiac filling pressure of this amount are not sufficient to affect the cardiac output consistently. Also if one examines closely the data on simultaneous estimations

of venous pressure and cardiac output (Table 2), the lack of correlation is readily seen. Calculation shows no significant correlation within the 30 pairs in which simultaneous changes in venous pressure and cardiac output could be compared. One must conclude that the increase in cardiac output is not to be attributed to an improvement in cardiac filling caused by increased blood volume.

cardiac function found. The results obtained on patient L.B. (the only subject with fever), Table 3, are in complete accord with this concept for the increase in cardiac output is closely related to the increased level of blood sugar. However, in patient J.Z. an even higher increase in blood sugar was not accompanied by a significant change in cardiac output and in L.G. (with hypertension) the fall of the blood

TABLE III.--THREE EXPERIMENTS SHOWING VARIOUS CHANGES AFTER GLUCOSE INJECTION

Case	Time	Pulse Rate	Blood		Cardiac Output	Plasma	Volume	Diagnosis
			Sugar	Chlorides				
			mg p. 100 cc.	M Eq/L	%	cc.	%	
1. L.B.	Before glucose	98	80					Pyrexia of unknown origin (T. 100-102°) Normal C V system
	After glucose 3 min.	106			+28			
	6 - 8 min.	103	243		+28	+443	+16	
	15-18 min.	102	223		+15	+455	+16	
	30 min.	100	196		+4	+274	+10	
	45 min.	100	176		+3	+553	+19	
2. J.Z.	Before glucose	62	78	103				Involutional melancolic. Normal C V system.
	After glucose 3-5 min.	62	254	102.1	+3	+406	+12	
	8 - 15 min.	61	199	102.5	+4	+230	+7	
	30 min.	60	188	102.8	-6	-27	-1	
	45-50 min.	60			-4			
3. L.G.	Before glucose	57	90	107.4				Hypertensive C.V. disease due to chronic pyelonephritis
	After glucose 3 - 5 min.	52	236	106.4	+9	+386	+9	
	8 min.	53			+15			
	15-16 min.	55	208	105.9	+9	+214	+5	
	30 min.	56	176	107.2	+9	+637	+13	
	45 min.	58	156	107.4	+10	+287	+6	

Therefore, the second alternative must be considered; glucose might increase the cardiac output by a direct stimulating effect on the myocardium. A large amount of data on the Intravenous Glucose Tolerance Test[6] indicated that after an injection such as was employed, blood glucose would be increased for the duration of the experiment. This was confirmed in 3 subjects and the correlation between the blood sugar level and the change in cardiac output per minute is significant. So glucose, present in excessive amounts, may well have caused the increase of sugar curve is not accompanied by a corresponding fall of cardiac output. Obviously other factors than the level of blood sugar influence the intensity of the cardiac effect which follows intravenous glucose.

The results show that the functional condition of the patient's cardiovascular system is one such factor.

Summary and Conclusions. Blood volume, peripheral venous pressure, blood sugar and blood chlorides have been measured before, during and after the increase in cardiac output follow-

ing the intravenous injection of 50 cc. of hypertonic glucose solution into healthy persons and cardiac cases. The results have been subjected to statistical analysis.

Although the blood volume increased after injection, and this was significantly correlated with the increase in cardiac output, the rise in venous pressure was almost negligible and no significant relation between the changes of venous pressure and the increase of cardiac output could be demonstrated. Therefore, no evidence was obtained that increased filling of the heart is an important factor in the cardiac stimulation which follows glucose.

Blood sugar increased markedly after glucose injection and the change in its level was significantly correlated with the increase in cardiac output. Blood chlorides remained constant. Therefore the increase in cardiac output is best explained as a direct action of glucose on the heart, analogous to that well known to occur in experiments on the hearts of animal preparations.

The intensity of the cardiac action of glucose varied inversely with the clinical estimate of cardiac capacity, the average effect being most prolonged in those patients whose functional capacity was lowest. This again appears to be analogous to results secured in acute animal experiments, in which the heart is more strongly stimulated by glucose when it is in poor condition.

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AMEBIASIS: EXPERIENCE IN THE JOHNS HOPKINS HOSPITAL, 1936-1946

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In 1903 Futcher[19] first reported the experience with amebiasis in the Johns Hopkins hospital, at which time that disease was shown to be responsible for 0.74% of the admissions to the medical service, with a mortality rate of 25.3%. Since that time great strides have been made in our understanding of the pathogenesis, complications and treatment of amebiasis. No attempt to review comprehensively the literature relevant to the disease will be made here, since Craig[11] has quite adequately done so to 1944. During and since World War II great emphasis has been placed on the possible sequelae of tropical exposure of masses of American troops and the fear of increased incidence of amebic disease in this country expressed.[2,26,36,50] Many more recent reports have dealt with military personnel in whom relatively acute amebiasis was present; it seems worth while, therefore, to review the experience of a large civilian hospital in dealing with this problem.

Material. In this review, all hospitalized adult patients in whom a diagnosis of amebiasis in any form was made during the period extending from 1936 to 1946 inclusive, were studied. A total number of 296 cases were catalogued, 0.15% of the total hospital admissions over the same period. Of these cases 15 were not available for analysis, 39 were inadequately studied, or the diagnosis not satisfactorily established, and 27 cases were diagnosed on services other than the medical service and were excluded. The remaining 205 cases, all proven amebiasis by (a) demonstration of *Endameba histolytica* in the stools, or (b) specific response to emetine in extra-intestinal forms of the disease, were carefully analyzed. This number constitutes 0.51% of the total number of admissions to the medical service during the period of study.

Endameba histolytica is a protozoan the laboratory identification and characteristics of which are beyond the scope of this review. Suffice it to say, it is primarily an intestinal parasite occurring in from 5% to 20% of the populace of this country, with an average over-all incidence of approximately 10%.[11,45] Extensive data have accumulated establishing the pathogenicity of this organism in man as well as in certain experimental animals.[2,11] The discrepancy between the incidence of infection and incidence of symptomatic amebiasis has not been clearly defined. It is felt by many that concomitant bacterial invasion is a prerequisite to symptomatic amebiasis, and, indeed, Craig thinks that all infestations are complicated by the presence of bacteria,[11] others that bacterial infection may lower the general resistance or facilitate entrance of the protozoan into the intestinal mucosa.[5,35] It is a prevalent concept that approximately 10% of the cases of amebiasis harbor organisms of the Shigella group.[12] In view of the frequency of non-specific symptoms, some workers have felt that the diagnosis of amebiasis should be made only in the presence of a complete therapeutic response to amebicidal drugs.[39]

For clinical purposes, the life cycle of *Endameba histolytica* is a relatively simple one, although detailed analysis of racial characteristics and related organisms makes its more definitive un-

derstanding somewhat intricate. It is felt that the most likely sequence of events is (1) ingestion of cystic form, which (2) excysts in the alkaline secretion of the small intestine with formation of metacysts which (3) by their cytolytic action invade the mucosa of the cecum from which (4) trophozoites further invade the submucosa or muscularis, occasionally the serosa, and may (5) be passed into the lumen to the more distal large bowel, where the process is repeated, or form typical amebic ulcers, and sometimes invade the venules or lymphatics, thus facilitating invasion of extra-intestinal organs.[11,17,26] Many local factors other than the bacterial ones mentioned above have been incriminated, including the total number of parasites, the pH of enteric secretions, the motility of the intestinal tract, the virulence of the parasitic strain, host-resistance, and others.[17] That symptomatic amebiasis occurs less commonly in children and more commonly in males and in the tropics has been established.[11]

Symptoms. The symptomatology of amebiasis is protean. Many infected persons are entirely asymptomatic, the incidence ranging from 14%[28] to 61%,[16] although most observers place the incidence of asymptomatic carriers between these figures.[2,11,25] In this series, twenty cases (10%) were entirely free of symptoms which could be attributed to the presence of *Endameba histolytica*. The smaller number of symptom-free cases in this study is possibly attributable to the fact that these were all hospitalized patients, usually with symptoms referable to the gastro-intestinal tract.

Craig[11] classified symptomatic amebiasis into (1) carriers with indefinite gastro-intestinal symptoms, (2) recurrent attacks of diarrhea, (3) chronic amebic dysentery and (4) those with complications. In this series 4.4% were considered to be carriers with non-specific gastro-intestinal symptoms which included indigestion, flatulence, abdominal discomfort, constipation, eructation, malaise, fatigue, headache, etc. Of these, constipation was most common, occurring in 65% of the cases. The remaining cases were thought to have symptoms attributable to amebiasis.

No attempt was made to ascertain the incubation period in this group, but it has been said to be quite variable, ranging from several days to many months.[26] The onset was usually insidious, although in approximately 10% of the cases it was acute and explosive, in most cases in association with a more severe form of the disease. This figure is in accord with previous estimates.[14] The most common symptoms are tabulated in Table 1. It is immediately apparent that in this group of symptomatic amebiasis diarrhea is the paramount symptom, occurring in 58.6% of the cases. The categories of mild, moderate and severe are purely arbitrary, patients with from 5 to 10 bowel movements daily being considered moderate and comprising the majority of the group of those with bowel frequency. Alternate diarrhea and constipation, emphasized so strongly by some,[2,17] occurred in approximately 12.5% of these cases, and if combined with those patients manifesting diarrhea alone would create a figure of 71.1% or nearly 3 in 4 patients giving a history of diarrhea. Abdominal pain has been said to be present in 95.4%[25] of cases of amebiasis, though in this study its incidence was 53%. It was most frequently described as cramping, intermittent, not uncommonly generalized, but more usually occurring in the lower abdomen or in localized areas of the abdomen. The periodicity of these symptoms was striking, only 10% to 15% describing continuous pain or diarrhea.

The quality of the stool in the history varied markedly, some described by patients as not abnormal, others as

profuse watery diarrhea. Gross blood was described by 27.8% of this group. Mucoid stools were described by 20.4% of the patients. Other less common symptoms are depicted in Table 1. Fever was described by 11.2% of those cases which were not complicated by extra-intestinal forms of the disease (in contrast to the 55% of those with hepatitis or abscess), a figure approximating that of Karl and Sloan,[25] and supporting the statement of Klatskin[28] that slight temperature elevation is frequent, but that "high fever almost invariably indicated a complication". Futcher[19] thought that fever usually was present at onset, but Craig[11] has not found this to be true. Urticaria, reported in 40% of one group[28] was not observed in this series.

The duration of these symptoms varied greatly, but the great majority (71.4%) exceeded 6 months, a fact probably to some extent responsible for the frequency of persistent symptoms following adequate therapy (*vide infra*). Only 3.4% were of less than 1 week's duration and 14% had symptoms, usually intermittently, for greater than 10 years, the longest duration recorded being 27 years (2 cases).

Of interest is the fact that 4 cases were subjected to appendectomy (3 in this hospital, 1 elsewhere) because of doubt about the origin of abdominal pain. This is a not uncommon source of confusion, and Craig[11] thinks that "in every individual presenting symptoms of appendicitis an examination of the feces should be made, and if found (*Endameba histolytica*) anti-amebic therapy should be tried before surgical means unless symptoms are such as to demand immediate operation". In one series, a third of the cases of appendicitis coming to operation were found to have amebiasis,[10] and Faust[41] states that 10% of cases of appendicitis have amebic involvement. It should be emphasized that if response to anti-amebic therapy in such cases is not prompt, surgical measures should be taken. Manson-Bahr,[31] in a large series of cases of amebiasis, found 5.4% coming to appendectomy and in none were *Endameba histolytica* found. Pathological examination of the appendices removed in this hospital showed no amebae, but treatment had been instituted in all cases prior to operation.

PHYSICAL EXAMINATION. It is a frequently emphasized fact that the most common physical finding in intestinal amebiasis is localized abdominal tenderness[2,4,11,25,26,28,36] usually about the cecum or sigmoid. In a large portion of this series the physical examination was entirely negative, although certainly the most common finding was abdominal tenderness, which was observed in 45% of the chronic cases and 65.5% of the acute; in the former, tenderness was most common in the right lower quadrant, although other areas, chiefly left lower quadrant and epigastrium, were frequently sensitive, and in the latter, generalized tenderness was usually observed. As has been shown by others[11,36] fever in the chronic cases is unusual, being found in only 2.9% of this series. Fever was observed in 50% of the acute cases, and whether this is due to secondary infection, as is believed by Craig,[11] or due to *Endameba histolytica* alone is impossible to state with assurance, although in no acute cases were pathogenic intestinal bacteria recovered, despite adequate bacteriologic study. That pyrexia frequently indicates a complication is evidenced by the fact that 66% of the cases of extra-intestinal amebiasis were febrile. Browne *et al.*[7] showed that fever occurred in 64% of complicated cases in contrast to 7.4% of uncomplicated ones. In 25% of the chronic cases in this series, thickened, easily palpable, sometimes tender colons were described. Craig's[11] statement that in every case in the chronic group weight

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loss occurs is not borne out by the recorded observations in this group that 9% appeared chronically ill and another 3% showed evidence of weight loss. Actually the preservation of adequate gross nutrition was striking, despite prolonged bouts of moderately severe diarrhea in many instances.

Opinion concerning indications for, and significance of, sigmoidoscopic examination vary widely; in his monograph Craig[11] states that this procedure should be reserved for cases in which stool examinations are negative, and that of all cases examined, less than 25% reveal lesions. On the other hand, typical discrete ulcers have been reported to occur in from 21% to 90% of cases,[36] approximately twice as often in symptomatic as in asymptomatic cases.[25] In contrast to Craig, Albright and Gordon,[2] feel that all cases should be proctoscoped. In this series, 61 patients were sigmoidoscoped and of these 37.7% revealed no abnormalities; those showing significant changes included: 21.3%, classical discrete undermined ulcers with normal intervening mucosa; 16.4%, diffuse hyperemia without visible ulceration; 11.0%, extensive involvement of the mucosa suggesting chronic ulcerative colitis; 10%, areas of spotty bleeding and mucoid discharge without fully developed ulcers; and 1 case was found to have a venous angioma in the sigmoid. In 8.2% of the proctoscoped cases the diagnosis of amebiasis was reached by the finding of *Endameba histolytica* in smears from the ulcerated areas, whereas in several of these cases repeated stool examination had previously been non-productive. The case in which the venous angioma was demonstrated suggests an additional reason for more frequent utilization of this procedure for the revelation of underlying lesions, such as carcinoma, polyps, lymphopathia venereum, and others, as well as facilitating the diagnosis of amebiasis.

TABLE I. SYMPTOMS IN UNCOMPLICATED INTESTINAL AMEBIASIS

	PER CENT OF CASES		PER CENT OF CASES
1 DIARRHEA - TOTAL	71.1	5 WEIGHT LOSS	14.6
MILD	12.5	6 FEVER	11.2
MODERATE	31.9	7 FLATULENCE	9.0
SEVERE	14.2	8 CONSTIPATION	7.4
ALTERNATING DIARRHIA AND CONSTIPATION	12.5	9 "INDIGESTION"	7.0
2 ABDOMINAL PAIN - TOTAL	53.0	10 ERUCTATION	6.9
MILD	22.1	11 ABDOMINAL DISTENTION	6.2
MODERATE	23.9	12 TENESMUS	5.0
SEVERE	7.0	13 FECAL INCONTINENCE	2.0
3 STOOLS - GROSS BLOOD	27.8	14 SYSTEMIC (HEADACHE, ANOREXIA, MALAISE, FATIGUE ETC	28.0
MUCOUS	20.4		
4 NAUSEA AND VOMITING	16.5		

LABORATORY DATA. Of laboratory procedures, examination of the stool is the only method by which a definitive diagnosis can be established (exclusive of extraintestinal amebiasis). It cannot be overemphasized that great technical skill and prolonged training are prerequisites to adequate examination of stool specimens. No physician without at least 6 months' training in the definitive identification of this parasite should attempt to perform such examination. Numerous techniques have been utilized in isolating the protozoa, from simple unstained smears of

the stools to elaborate cultural methods. In this laboratory it is felt that a minimum of 6 stools should be examined, utilizing unstained smears or wet stains with Quensel's stain for trophozoites in loose stools and zinc sulfate flotation for cysts in formed stools. These preparations frequently need not be stained, but, if necessary, hematoxylin is adopted. Ameba cultures are reserved for those cases in whom several stool examinations are negative and in whom the disease is clinically suspected, or occasionally for confirmation of the diagnosis in the presence of cysts or trophozoites of uncertain nature; however, it is felt that *E. coli* may occasionally take on the characteristics of *E. histolytica* in culture and that the diagnosis should be made from direct stool examination whenever possible. Purging is recommended by some to facilitate diagnosis, and this procedure is utilized in this hospital after several negative stools are obtained and clinical suspicion persists. It must be remembered that purging may hinder the demonstration of the organism for several subsequent days.[28] A frequently overlooked fact is that, not uncommonly, previously administered barium or bismuth may temporarily eliminate *E. histolytica* from the stools.[2] Differentiation of the *E. histolytica* from other intestinal protozoa is beyond the scope of this paper, but the difficulty is obvious when one realizes that 32% of these cases had concomitant infestation with *E. coli, E. nana* or *Dientameba fragilis*.

Gross examination of the stool revealed that in 34% liquid or semi-liquid stools were passed by the patient on admission; the remainder were formed. Gross blood was observed in only 15 cases (8%), a figure considerably below the incidence described by the patients (*vide supra*), but tests for occult blood were positive in 20.5% of the cases. In the great majority of these cases stool cultures for intestinal bacterial pathogens were performed, and in only 4 cases (2.3%) were the results productive, in contrast to the oft-quoted figure of 10% offered by others.[2,12]

Anemia (hematocrit below 36), thought to be common by Futcher,[19] was found in only 5% of uncomplicated cases, although it occurred in 50% of those with complications. Likewise, leukocytosis exceeding 12,000 was present in only 5% of cases in whom it could be accounted for by no other means, though 65% of those with hepatic complications revealed a leukocytosis, usually with a shift to the left in the hemogram. Eleven cases (6.2%) demonstrated an otherwise inexplicable eosinophilia (greater than 10%), a fact that is in accord with other reports[11] in which the rarity of eosinophilia is encountered and with the statement that one must suspect co-incident infestation with helminths when this finding is noted.[2] Elevation of sedimentation rate was noted in 22% of uncomplicated cases in contrast to the statement of Klatskin[28] that this test is usually normal. In hepatic complications, sedimentation rate was elevated in 30% of cases, a figure considerably below the 81% quoted by Klatskin.[28]

The complement fixation test, found by Craig[11] to be highly specific, was employed in only 5 of these cases and in every case it was negative. This result lends support to the statements of others that with present technique incomplete reliance can be placed on this test.[33,41] When a more satisfactory antigen is available, this test should be a most useful instrument, as emphasized by Craig. Attempts to correlate agglutinations of *E. histolytica* cysts with infection have been unsuccessful,[20] and to date the complement fixation is the only serologic test of any degree of usefulness.

Barium enemata were carried out in 74 cases in this series. Of these 25

(34%) were entirely normal. The remaining 66% revealed abnormalities: (a) mucosal pattern, usually in the region of the cecum or sigmoid, although several revealed more extensive involvement, (b) 24% were reported as showing a "spastic colon"; (c) the remaining 9% revealed various evidences of abnormality, including polyposis, diverticulosis and chronic ulcerative colitis. The most characteristic Roentgen-ray changes are said to be cecal irregularity and deformity with incompetence of the ileocecal valve.[36] Incidence of abnormal findings have been variously recorded from 26%[20] to 100%[40] and our figure falls within this range. Craig[11] feels that barium enema cannot be accepted as of much value; but our experience in which 9% of the cases demonstrated other abnormalities of significance would lend support to the feeling expressed by Browne *et al.*[7] that (1) a negative barium enema is helpful in eliminating other diseases, (2) finding of typical changes tends to support the diagnosis and (3) finding of granulomatous changes which respond to anti-amebic therapy is "assuring". Roentgen-ray examination of the chest is almost universally accepted as being of value in cases of hepatic and pulmonary involvement[11,27,44,48] where changes ranging from elevation and fixation of the right diaphragm to extensive pleural and pulmonary involvement are observed. In this series, 80% of cases of hepatic involvement in which a chest roentgenograph was made revealed elevation and fixation of the right diaphragm with or without atelectasis in the right lower lobe, a figure approximating that of Sodeman and Lewis (81%).[48]

Other laboratory studies were of inconstant value. Abnormalities of the urine were found in 12% of cases with hepatic lesions (albuminuria, occasional hematuria, pyuria, cylinduria), but in only one intestinal amebiasis was albuminaria which was otherwise inexplicable encountered. Tests of liver function revealed significant abnormalities in 35% of those cases with liver involvement. Agglutinations for enteric pathogenic bacteria were positive in only 1 case, though performed in most, and 4 patients showed an unexplained monocytosis (11% to 16%). In no case were eosinophils reported in the stools, although Futcher[19] reports that this finding was present "in many cases." Charcot-Leyden crystals are said to be suggestive of *E. histolytica*,[11] but were described in no case in this series.

Complications. *Endameba histolytica* is capable of invading practically all tissues and organs, but invasion occurs as secondary involvement to primary intestinal disease in the great majority of cases. Involvement of the liver is the most common of the more serious complications. The correlation between liver abscesses and *E. histolytica* was first pointed out by Councilman and Lafleur,[10] but it remained for Rogers[44] to clarify the distinction between hepatitis and abscess formation. The protozoan may reach the liver by (a) direct extension from the bowel wall, (b) lymphatic spread or (c) via the portal vein, and after reaching this organ produces colliquative necrosis and disintegration with invasion of surrounding parenchyma by motile amebae.[37] Liver involvement occurs in from 22% to 55% of cases at autopsy, though clinically from 1.8% to 21% of cases of amebiasis have recognized hepatic lesions.[11] It is probable that many cases of hepatitis and abscess are unrecognized, since autopsy experiences indicate a significantly greater incidence,[11,44] though it must be said that many fatal cases of amebiasis occur on the basis of liver involvement. That hepatic manifestations may occur independently of gastro-intestinal symptoms is common knowledge, though by correlating clinical and autopsy evi-

dence of enteric disease Rogers[44] found that 96% of hepatic cases had concomitant intestinal amebiasis. The striking predominance of males (86.7%[44]) has never been adequately explained. A history of preceding diarrhea is obtained in from 25%[48,50] to 85%[11] and *E. histolytica* is found in the stool of 11% to 78%.[37] In one series approximately 50% had, clinically, abscess formation, the remaining being considered hepatitis.[47] In this series, 20 cases (10%) demonstrated liver involvement, and of these, 17 were considered hepatitis, 3 amebic abscesses; 75% of these cases were found to have *E. histolytica* in the stool, though frequently only after exhaustive search, and 45% gave a history of antecedent diarrhea, one as long as 8 years prior to the development of hepatitis.

Klatskin[27] classifies amebiasis of the liver into (a) acute amebic liver abscess, (b) acute amebic hepatitis, (c) sub-acute amebic hepatitis, (d) chronic amebic hepatitis, (e) chronic amebic abscess, though in his series none of the latter were observed. In this series, there were 4 cases of acute hepatitis (20%), 6 cases of subacute hepatitis (35%), 5 cases of chronic hepatitis (25%), and 3 liver abscesses, all of which could be considered subacute. Ochsner and Debakey[37] tabulate symptoms of amebic involvement of the liver as fever (84.5%), local pain in the region of the liver (75% to 100%), nausea and vomiting (22.1%), weakness, anorexia, and others (52.2%), jaundice (10.5%). In this group fever was present in 66%, pain in the region of the liver in 85% and jaundice in only 5%. The pain was frequently sudden in onset and exacerbated by respiratory effort. Its intensity varied with the duration, usually being more severe in the acute hepatitides, and continuous in most cases, irrespective of the duration. It is interesting to note that 4 cases (20%) had been treated prior to the development of hepatic complications with anti-amebic drugs, usually 6 months to 2 years prior to the development of hepatitis, yet these cases were stool positive on admission to this hospital. Physical findings could be closely correlated with the symptoms, all of these cases appearing acutely or chronically ill, 85% revealing liver tenderness, and 80% hepatomegaly, (figures which approximate those offered by other observers)[27,37]. 35% showed signs of atelectasis, some with pleuritis, at the right lung base, and all were found to have splinted and elevated right diaphragms, frequently with bulging in the right lower interspaces. The frequency of pleurisy with or without effusion in association with amebic hepatitis has led Carruthers[8] to suggest that any patient demonstrating tender hepatomegaly, high diaphragm and

TABLE 2. PHYSICAL FINDINGS IN UNCOMPLICATED INTESTINAL AMEBIASIS

ACUTE		CHRONIC
	ABDOMINAL TENDERNESS	
65.5%	*TOTAL*	45.0%
50.0%	*GENERALIZED*	9.0%
0.0%	*LOCALIZED RLQ*	17.0%
16.5%	*OTHERS*	19.0%
16.5%	ABDOMINAL DISTENTION	5.0%
0.0%	UNDERNOURISHED, CHRONICALLY ILL	9.0%
16.5%	PALPABLE, THICKENED COLON	26.0%
50.0%	FEVER	2.9%

pleurisy warrants anti-amebic therapy. Amebic abscesses may rupture into the pleural cavity, parenchyma or bronchus of the lung, peritoneal cavity, pericardium, stomach, large or small bowel, lumbar muscle or skin, giving rise to the dire complications which are self apparent, though the prognosis after rupturing into a bronchus is less grave than that into a closed cavity.

Primary amebiasis of bronchi and lung has been said to occur,[11,15] but pulmonary involvement is almost always secondary to hepatic disease. An almost universally fatal complication of amebiasis is metastatic involvement of the brain, which fortunately is rare, giving rise to symptoms and signs of a cerebral abscess. Two such cases were observed in this series (1% of the total), one of which died after extension into the meninges, with the development of a rapidly fatal meningitis, the second of which was a presumptive diagnosis, and unfortunately was not followed in this hospital.

Amebic granulomata are not uncommon and may simulate carcinoma of the large intestine,[3,11,30,42] sometimes causing intestinal obstruction, abscesses or perforation. These lesions may require surgical removal[30] and it is felt by some they may lead to malignant degeneration; Read and Anderson[42] report 4 cases in which carcinoma of the large intestine followed or accompanied amebic infection. In this series, 1 case of presumed amebic granuloma was seen and 4 cases of amebiasis in whom adenocarcinoma of the colon was found. Amebiasis may frequently involve the appendix, simulating acute appendicitis (*vide supra*), but may also simulate other causes of an acute surgical abdomen. One case in this series of amebic peritonitis was observed, although the primary site of involvement of the peritoneum was not ascertained despite 2 laparotomies. This complication may arise from hepatic or intestinal invasion.

Other complications include perforation, massive intestinal hemorrhage, amebic cholecystitis, splenitis, urinary tract involvement, gastritis, enteritis,[11] arthritis,[40] prostatitis[4] and others, none of which were observed in this series.

The most common complication in this group was the development of chronic intestinal symptoms including chronic ulcerative colitis, regional enteritis, and others. Of this series of 205 cases, 88 were adequately followed after discharge from the hospital; however, 18 cases (8.8%) had persistence of symptoms while in the hospital, despite treatment which was successful in elimination of *E. histolytica* from the stools. Five patients in whom the picture of chronic ulcerative colitis was absent on the first admission, proceeded after therapy to develop the classical features of this disease, and another 7 had developed this syndrome prior to admission in a manner suggesting the possibility of an etiologic connection with amebic infection, giving a total of 12 cases (5.9%) in which chronic ulcerative colitis developed. Another group of 18 underwent a relapse following discharge and on readmission 5 were found to be stool positive; an additional 4 cases gave a history of adequate anti-amebic therapy elsewhere prior to admission to this hospital, and were found to be stool positive here. A total, therefore, of 52 cases, approximately 25% of the entire group of 205 cases, noted persistence or recurrence of severe intestinal symptoms (cases with persistent mild diarrhea were excluded) following what was assumed to be adequate therapy, although only 5 cases (2.9% of those who were actually given anti-amebic therapy) underwent stool positive relapse, or reinfection.

Diagnosis. The diagnosis should be suspected in all patients with intestinal symptoms; it is established, however,

only by (1) the finding by direct examination or culture of *Endameba histolytica* in the stool, urine, sputum, draining sinuses, etc., or from other tissues, or by (2) the emetin therapeutic trial in extra-intestinal involvement. The diagnosis can be strongly suspected in the presence of a positive complement fixation test, but the organism must be demonstrated for a definitive decision. The disease in which differential diagnosis is necessary most frequently is bacillary dysentery, and the accompanying table (Table 3) modified from Craig[11] outlines the essential differential features.

TABLE 3. DIFFERENTIAL DIAGNOSIS FROM BACILLARY DYSENTERY
MODIFIED FROM CRAIG[2]

AMEBIC	BACILLARY
CHRONIC, ENDEMIC	ACUTE, EPIDEMIC
INCUBATION – DAYS TO YEARS	INCUBATION USUALLY < 1 WEEK
USUALLY INSIDIOUS ONSET	ACUTE ONSET
SYMPTOMS INTERMITTENT	CONTINUOUS, DURATION FEW DAYS
MAY DEVELOP HEPATIC INVOLVEMENT	LIVER RARELY INVOLVED
COLON THICKENED WITH LOCALIZED TENDERNESS	GENERALIZED ABDOMINAL TENDERNESS
MODERATE OR NO TENESMUS	SEVERE TENESMUS
RARE, IF ANY, ARTHRITIS	ASSOCIATED ARTHRITIS NOT UNCOMMON

TREATMENT. Every case, irrespective of symptomatology, deserved adequate treatment,[11,25] in view of the known tissue invasion and the possibility of serious complications. The treatment of choice remains somewhat problematic.

Since Rogers[43] hailed emetine as a specific curative agent in this disease three-and-a-half decades ago, this drug has probably been the most extensively used of the amebicides. It is a generally accepted fact that parenteral emetine acts largely on tissue forms and is not successful in eliminating intestinal amebae. That it is the drug of choice in extra-intestinal amebiasis is undisputed (although in a recent report, it was shown by Conan[9] that chloroquine was effective in curing all of a small series of hepatitides) and in all cases of hepatitis, emetine therapy should be instituted prior to surgical procedures.[3,27] Opinion concerning its use in intestinal amebiasis is divided; some feel that emetine should never be used in uncomplicated intestinal disease,[4,26] though most observers feel that it is useful in alleviating the symptoms of acute amebiasis;[7,13,18,28,45] many feel that in view of the known tissue invasion in all cases, emetine should routinely be combined with iodine or arsenical compounds.[2,13,25] More recently emetine administered orally in enteric coated tablets has been found highly effective and free of significant toxic effects in a small series.[46] Emetine in combination with bismuth and iodine (EBI), has been found the most useful medicant by the British.[1,19,31] Emetine is a toxic drug, the action of which is cumulative and the frequency of untoward side effects is widely recognized, and, for that reason, it must be used with caution. *Endameba histolytica* has been shown to become resistant to emetine[18,22] and Manson-Bahr feels that the widespread use of emetine during the war years has been a major factor in producing refractory cases of amebiasis.[31] In this series, emetine alone was used in only 5 cases, 3 of whom had persistent diarrhea following treatment, and one of whom was not followed, although these

cases became, temporarily at least, stool negative. Eight cases gave a history of previous emetine therapy and were found here to be stool positive. No untoward effect was observed in any case treated with emetine except transient electrocardiographic changes in 2 cases and occasional local irritation.

The iodine-containing drugs, chiniofon, diodoquin and vioform have been found to be of great usefulness in treating uncomplicated amebiasis, iodine being a direct amebicide. That the iodine in the compounds is absorbed has been shown by the use of the radioactive element in chiniofon.[3] The therapeutic efficacy of these drugs ranges from 88 to 99%,[12,18] when used alone. The incidence of toxicity is negligible, except for occasional diarrhea observed with chiniofon *(per os)*. Slight diarrhea was seen in 4 cases in this series who were treated with chiniofon, none in those treated with vioform or diodoquin. Accurate evaluation of their efficacy in this series is impossible since the great majority were combined with emetine or arsenicals, though no stool positive relapses were observed except in one case in which Yatren (chiniofon) was used by retention enema in combination with parenteral emetine.

Arsenic, likewise a direct amebicide, has been used in various forms in the treatment of amebiasis, but by far the most satisfactory, and least toxic form is carbarsone, either orally or by retention enema. Satisfactory results have been obtained in from 75 to 95% of cases.[11,17,18,32] Faust[17] has found carbarsone to be only 75% as efficacious as chiniofon and the greater incidence of toxic reactions must not be overlooked,[31] particularly in the presence of liver disease. It is felt by some that arsenical therapy in combination with iodoquinolinic medicaments is the most satisfactory mode of therapy.[13]

Combined therapy with several of the above-mentioned drugs has been used in our series and the variations in the method have been so extensive that statistical studies of each combination would be insignificant. However, the overall results in elimination of the organism by utilizing several drugs have been gratifying (2.9% relapse), although not superior to that obtained in the small number of this series in which arsenical or iodoquinolinic therapy alone was used.

Many other drugs have been used in this disease including Kurchi-bark, emetineperiodine, amemitine, chaparra amargosa, bismuth sub-nitrate,[11,31] trilactic acid,[49] and penicillin,[29] but results have been inferior to date to those obtained with the more conventional drugs.

In view of the frequency of secondary bacterial invasion, it has been frequently suggested that sulfonamide and, or, penicillin (and we might add, streptomycin) be used,[15,23,45] and this seems to be based on logical reasoning. In this series, such therapy was used in no instance, although it is conceivable that in certain fulminating cases antibiotic or chemotherapeutic agents should be a useful adjunct to amebicidal therapy.

Mortality. In contrast to the mortality rate prior to the institution of modern therapy (Futcher, 23.5%),[19] the prognosis is now regarded as excellent, usually depending on the basis of complications,[11] and, if early diagnosis and treatment are established, fatalities should practically be abolished. In this series, the total mortality was 3.3%, of which only 1.4% (3 cases) could be attributed to amebiasis. All cases were not followed adequately after treatment, and it is possible that the mortality might be somewhat higher. Of those deaths in which *E. histolytica* could be incriminated as the responsible agent, 1 died of liver abscess, complicated by cerebellar abscess and meningitis, 1 of persistent amebiasis

with severe chronic diarrhea not responding to repeated courses of amebicidal therapy and ileostomy, and 1 with the classical picture of regional enteritis. The remaining 4 deaths were due to Hodgkin's disease (one), teratoma (one), and adenocarcinoma of the colon (two). Autopsy was obtained in 6, all of whom had adequate antiamebic therapy, and no amebae were demonstrated in 5 although present in the case with the cerebellar abscess.

COMMENT. This analysis of 205 cases of proven amebiasis has reaffirmed previous reports in which the protean nature of the disease with its varying clinical course and frequent paucity of physical findings have been described. Diarrhea has been shown to be the foremost symptom and localized abdominal tenderness the most common physical finding. The incidence of complications has approximated the classical figures, that of hepatic involvement being foremost, and extension to the lungs, peritoneum, brain and elsewhere less common. The diagnosis is made on the basis of demonstration of *E. histolytica*, or a rapid therapeutic response to emetine. Treatment is probably best accomplished by the use of iodoquinoline compounds in uncomplicated amebiasis. Emetine should be reserved for severe dysentery (for symptomatic control), and extra-intestinal involvement, although one could not be condemned for combining emetine with arsenical or iodine compounds if so desired, and the combination of more than one drug is indicated in resistant cases. It cannot be overemphasized that all patients harboring the organism deserve adequate therapy, and all treated cases should be followed with serial stool studies and treatment reinstituted if relapse occurs. It appears that the feeling expressed by Adams[1] that the actual preparation of drugs is less important than the period of time over which a number of drugs is given can be supported.

That certain cases of amebiasis become intractible to all therapy has long been recognized,[1,6,11] and in this series one patient died of what seemed to be intractible amebic disease. On the other hand, the persistence of diarrhea, abdominal pain and other symptoms suggestive of the persistence of amebiasis, in the absence of demonstrable protozoa in the stools, has likewise been frequently catalogued.[2,11,13] In this latter group, it may sometimes be difficult or impossible to distinguish the postamebic intestinal changes, from the co-incidental occurrence of amebic infection in patients with spastic or mucous colitis or chronic non-specific ulcerative colitis. The most striking result of this study is the fact that in 25% of the cases, gastro-intestinal symptoms of moderate to severe degree persisted after what is assumed to be adequate therapy, and that of these 5.9% developed or had developed the features considered diagnostic of chronic ulcerative colitis, namely, proctoscopic and Roentgen-ray changes with persistent chronic bloody diarrhea.

The high incidence of infection in asymptomatic carriers engenders doubt in the minds of some that the chronic diarrhea seen after eradication of the organism is the result of its presence previously in the tissues,[39] and others feel that "many patients become bowel invalids because of a neurogenic tendency."[4] That amebiasis may result in chronic ulcerative colitis has been previously shown[6,13,45] and it has been suggested that all cases of chronic ulcerative colitis be given a trial of antiamebic therapy.[36] In one group of 140 cases, 29.1% demonstrated persistence of diarrhea in the presence of negative stools, a figure approximating the 25% of this series. Craig[11] emphasizes the fact that single attacks of amebiasis usually show no complication compar-

able to this, whereas "frequently" those persons with repeated attacks develop chronic diarrhea which . . . "may imitate sprue." Howard[24] found that 73% of a small series of ameba "carriers" underwent symptomatic relapse after adequate therapy.

The difficulty involved in clearly distinguishing those cases of "spastic colon" with concomitant amebic infestation from the cases in which irreversible intestinal changes have developed on the basis of amebic activity is apparent. That post-amebic colitis exists is not disputed, but that careful study is necessary to establish its presence is emphasized. Careful scrutiny of the histories of those patients who had developed by the time of admission, or subsequently developed, chronic ulcerative colitis reveals evidence that in at least 9 of the 12 cases, the history and physical findings, correlated with the original proctoscopic examination, strongly suggest an amebic pathogenesis of the chronic disease of the colon wall. In 3 cases the evidence was equivocal. The majority of cases demonstrated temporary improvement in symptoms and in proctoscopic findings coincident with anti-amebic therapy, only to relapse at a later date without evidence of *E. histolytica* in the stools.

Of the remaining 19.1% of our patients, in whom abnormal intestinal symptoms persisted, usually intermittent diarrhea and abdominal pain, many have received subsequent courses of amebicidal drugs, frequently with temporary improvement, though symptomatic relapse was forthcoming, and in these patients proctoscopy revealed either normal mucosa or diffuse hyperemia. Nine cases (4.4%) had disease of the large intestine which could account, at least in part, for the symptoms, 8 diverticulosis, 1 polyposis; but the remainder had no evidence demonstrable of other disease processes. Further therapy was notably unsatisfactory in this group. In 16% of the group with persistent symptoms, it was felt that a large personality element was involved, and the patients were discharged with diagnoses of "gastro-intestinal neurosis," "spastic gastro-intestinal tract," and the like, although symptoms referable to the gastro-intestinal tract prior to the onset of symptoms which suggested amebiasis were usually absent. Unfortunately, definitive personality studies were not carried out in the great majority of these patients.

The fact that 25% of the patients seen in this hospital in whom amebiasis was diagnosed continued to have symptoms after treatment demands that, in the future, careful study of personality, large bowel mucosa, and therapeutic response be made in all cases harboring this parasite. Follow-up studies must be cautious and prolonged, and therapy reinstituted in the presence of a relapse. Care must be taken to avoid over-treatment with emetine and to provide proper general medical and hygienic care with special emphasis on avoiding the "bowel consciousness" attendant on the development of such a disease, and psychiatric therapy instituted when necessary, though it seems probable from this study that the personality factors are less prominent in persistent post-amebic diarrhea than has been emphasized by some.

SUMMARY. 1. The 205 cases of proven amebiasis seen in The Johns Hopkins Hospital in the period extending from 1936 to 1946 inclusive have been reported.

2. The symptoms, physical findings and laboratory data have agreed relatively closely with those previously described.

3. The incidence of post-amebic stool-negative diarrhea has been shown to be 25% and the total incidence of development of chronic ulcerative colitis to be 5.9%.

4. More careful case analysis and follow-up studies in large series of patients with amebiasis are encouraged.

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SUBACUTE THYROIDITIS, STRUMA FIBROSA, STRUMA LYMPHOMATOSA: A CLINICAL-PATHOLOGICAL STUDY

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The subject of non-suppurative thyroiditis has been of interest mainly to the surgeon and pathologist because the diagnosis has usually been made only at the operating table or in the pathologist's laboratory. Indeed no necessity for distinguishing between the various forms existed since the therapy for all forms of thyroiditis was the same; *i.e.* thyroidectomy. We believe that it is possible to distinguish one group of cases—subacute thyroiditis—in which the diagnosis can be made preoperatively with reasonable certainty and in which operation may not be necessary.

Cases of non-suppurative, nonspecific thyroiditis have been broadly classified into Hashimoto's struma (struma lymphomatosa) and Riedel's struma (struma fibrosa) after the two men who first carefully described the pathological and clinical manifestations of the respective conditions. Generally included in with the struma fibrosa group, either as a recognized named variant or not, is a third group of cases, first studied in detail by DeQuervain[5] in 1904 and carefully reviewed and classified by him in 1936.[6] This group has been variously titled subacute thyroiditis, giant cell thyroiditis or pseudotuberculous thyroiditis according to whatever characteristic impressed the particular pathologist reviewing the slides. It is this last group of cases that we believe forms a distinct pathological and clinical entity, and is not merely a stage in the formation of an eventual struma fibrosa. This view was expressed originally by DeQuervain[6] and more recently by Crile.[3]

A word of historical clarification might be in order concerning Riedel's struma. In 1896 and 1897 Riedel[22,23] described 3 cases of "iron hard" thyroid enlargement which he wished to distinguish from carcinoma. Following thereafter other similar cases were reported by Tailhefer,[29] Silatschek,[27] Spannous[28] and Carle.[12]

When therefore in 1910 Riedel[24] presented a 15 year follow-up of 1 of his original cases he could describe a typical case as one occurring in a young individual who would present signs of a subacute enlargement, and induration of the thyroid accompanied by severe dyspnea. Duration of symptoms was short; 6 weeks, 8 to 10 weeks and 6 months in the 3 original cases. All patients were afebrile and all goiters were non-tender.

The original microscopic descriptions were not very detailed, mentioning only an accumulation of round cells and spindle cells which appeared to crowd out the normal follicles, a slight endarteritis and a rapid growth of young connective tissue. From this, it is quite apparent that he did not describe the painful, febrile type of thyroid enlargement which characterizes subacute thyroiditis. If we wish to be

accurate in our classification, we should limit the term Reidel's struma to those cases conforming most closely to the clinical and pathological description mentioned, with the realization that many unrelated conditions will be included until discovery of etiological factors makes classification more rational.

In 1912 Hashimoto[11] described another form of diffuse enlargement of the thyroid gland characterized microscopically by diffuse lymphocytic infiltration and destruction of acinar elements. He distinguished this condition from the specific thyroiditis, syphilitic, tuberculous, et cetera, and also from Riedel's struma.

Ewing[8] in 1922 expressed the opinion that Riedel and Hashimoto had described different stages of the same disease. This view held sway until Graham[9] in 1931 reviewed the 104 reported cases that could be found and by contrasting the clinical courses concluded that the two conditions were clinically and pathologically distinct. Since then reviews by Joll,[14] Clute and Eckerson,[2] McClintock and Wright,[20] Lee,[16] McSwain and Moore,[21] Graham,[10] Crile,[3] Schilling[25] and Marshall[18] have thrown the balance of opinion in favor of this later view. Particularly convincing is the fact that several authors[2,14,20,25] have reported cases of struma lymphomatosa, with further operation after intervals up to 4 years in which the microscopic picture underwent little or no change. However, it must be admitted that some glands are encountered which have characteristics of both conditions and suggest that a borderland between the struma lymphomatosa and fibrosa may exist. Graham[10] in 1940 stated that "the microscopical findings alone are not sufficient to distinguish between Hashimoto and Riedel's or between these and certain cases of exophthalmic goiter, chronic inflammation, degeneration and fibrous replacement in and around adenomata and involutional changes in senility."

From 1595 thyroidectomies performed in the past 8 years, we have selected 24 cases of non-specific thyroiditis and find that they follow the

TABLE I. -- SUBACUTE THYROIDITIS

		Microscopic Pathology					
						Infiltration	
	Type of Involvement	Tubercles	Giant Cells	Fibrosis	Lymph follicles with germinal centers	Lymphocytes & Plasma cells	Polys
M.B.	D	Numerous	Numerous	Dense	0	Numerous	2+
M.M.	D	Numerous	Numerous	Dense	0	Numerous	3+
*C.G.	D	Moderate	Moderate	Dense	0	Numerous	1+
G.J.	D	Numerous	Moderate	Dense	occ.	Numerous	0
**S.N.	L	Numerous	Numerous	Mod. dense	0	Numerous	3+
M.L.	L	Numerous	Numerous	Dense	occ.	Numerous	2+
D.H.	D	Numerous	Numerous	Dense	0	Numerous	3+
S.G.	D	Numerous	Numerous	Dense	0	Numerous	4+

D = Diffuse
L = Localized

*Small adenoma present
**Colloid adenoma present

following 3 subgroups: Pseudotuberculous subacute thyroiditis, struma fibrosa and struma lymphomatosa. An illustrative example of each is presented.

PSEUDOTUBERCULOUS, SUBACUTE THYROIDITIS—8 CASES, INCIDENCE 0.5%.

Clinical Characteristics. These patients usually have no previous history of thyroid dysfunction or of any other endocrine disorder. The age range is wide, from 10 to 65 years, in the cases of DeQuervain, the largest number occurring in the second to fourth decades. Our cases in this group range from 36 to 61 years, averaging 43 years. Females predominate in this series 7 to 1. Crile's[3] cases showed a 6:1 ratio and DeQuervain's a 2:1 female-male ratio. Only 2 of the women were postmenopausal, surgically induced in both. Four of the women had had pregnancies in the past. Symptoms of local and systemic disease were present though the former predominated. Pain, in the thyroid region of the neck or in the pharynx or referred to the ear, was the outstanding symptom in all cases and in 6 of the 8 cases was the initial symptom. Associated with the pain was a tender enlargement of the thyroid, either diffuse or localized, and symptoms of tracheal pressure such as hoarseness, cough, choking sensations, pain on swallowing and dysphagia. Fever, at some time during the course of the illness, appeared as the most common sign of systemic disease, being present in 6 cases. Of the 6 febrile cases, the pyrexia was present at the onset, in 3 cases, and 4 were febrile at the time of operation. Nothing characteristic was found in the temperature curve. One patient ran a spiking temperature to 104 daily, others stayed consistently at 101 to 102. Duration of fever was from 2 days to 8 weeks. A significant weight loss of 10 to 12 lbs. was noted in 5 cases. Only one patient presented clinical evidence of hyperthyroidism including nervousness, pal-

TABLE II. - ANALYSIS OF 24 CASES OF NON-SPECIFIC THYROIDITIS

	Subacute Thyroiditis	Riedel's Struma	Hashimoto's Struma
Cases	8	7	9
Age Range	36-61 years. Average 43 years	37-53 years. Average 46 years	6-53 yrs. Average 38 yrs.
Post Menopausal	2 cases	5 cases	3 cases
Symptoms Duration	2 weeks to 1 year	6 weeks to 3½ months	2 months to 20 years
Thyroid enlargement	Moderate in size, invariably tender	Relatively rapid growth, non-tender and bulky	Slow growing, bulky and non-tender
Pain	Present and severe in almost all cases	Absent in all cases	Absent in all cases
Tracheal pressure	Present in some form in all cases and moderate	Present in only 2 cases	Present in 1 case
Fever	Present at some time in almost all cases	Absent in all cases	Absent in all cases
Weight Loss	Present in the majority of cases, usually 10-12 lbs.	Present in only 1 case	Present in only 1 case
Preoperative thyroid dysfunction	Hyperthyroidism in 1 case	Hypothyroidism in 2 cases	Absent
Signs	Firm, or hard, tender, bilateral enlargement, 2-3 x normal size	Firm, hard, nodular, bilateral, non-tender enlargement	Firm, bilateral, non-tender enlargement
Laboratory Data	Sedimentation rates elevated. PBI elevated moderately. Low serum cholesterols	Low BMR's in 2 cases	No abnormalities
Operative Findings	Gland usually adherent to muscles, friable and poorly vascularized	Gland usually deeply fixed to surrounding muscles, firm fibrous and avascular	Firm, nonadherent gland
Pathology	Average amount of tissue removed 24 gm. Dense cellular connective tissue. Well formed tubercles with giant cells and histiocytes and small round cells. Clusters of polymorphonuclears.	Average amount of tissue removed 42 gm. Massive destruction of thyroid acini. Increase of interacinar connective tissue. Dense plasma cell and round cell infiltration	Average amount of tissue removed 57.7 gm. Diffuse, dense infiltration by lymphocytes with numerous follicles. Marked acidophilic degeneration of acinar cells
Therapy	Thiourea derivatives, x-ray therapy Thyroidectomy	Conservative thyroidectomy	Subtotal thyroidectomy

pitation, tremor and heat intolerance, which preceded the onset of fever by several weeks. The details are given later in Case 1. The duration of symptoms ranged from 2 weeks to 1 year, with 6 cases less than 2 months.

At physical examination, the thyroid was usually found to be enlarged 2 to 3 times the normal size, either firm or stony hard, and invariably tender. Bilateral involvement was apparent in 6 of the 8 cases. No enlarged cervical lymph glands were ever palpated. In only 1 case was the trachea clinically deviated from the midline. In one other case, the skin of the neck was red and warm. Laboratory data yielded little valuable information. Sedimentation rates, when done, were markedly elevated. White counts were slightly increased. Four patients who were febrile during hospitalization had elevated BMR'S of +7, +24, +30 and +55. Serum cholesterol determinations in those 4 cases were 132, 174, 141 and 141 per 100 cc. respectively. Kline tests when done were negative.

At operation the glands encountered were pale gray and very hard. Some were described as woody and others as stony hard or cartilaginous in consistency. In 5 of the cases, the thyroid was adherent to surrounding muscles. In 4 cases the gland was described as friable or brittle and in 3 cases poor vascularity was commented upon. A bilateral subtotal thyroidectomy was done in all but 1 case. The postoperative course was invariably uneventful. Follow up examinations were unfortunately not obtainable.

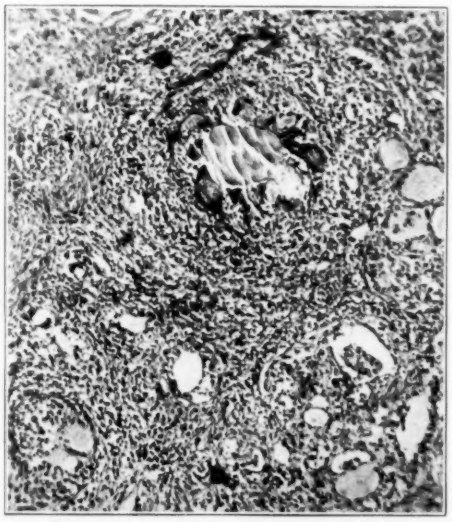

FIG. 1 A.—Subacute Thyroiditis: A typical tubercle consisting of a surrounding zone of round cells and dense connective tissue and several multinucleate giant cells radially arranged about a central drop of colloid (X 84).

Etiology: The etiology of the disease is completely obscure. The work of the past is difficult to unravel since the condition when encountered clinically and allowed to subside spontaneously has been called acute or subacute nonsuppurative thyroiditis. Yet the same syndrome when operated upon has been called Riedel's disease. Thus DeCourcy[4] in discussing the role of perithyroiditis in the etiology of what he supposed to be Riedel's struma was actually studying 2 cases of non-sup-

purative thyroiditis. Crile,[3] on the other hand, demonstrated by biopsy his view that the two conditions were identical. All attempts to isolate a bacterial agent have been unsuccessful. Blood cultures during the acute stage of 1 of our cases were uniformly negative. It is also hardly conceivable that a febrile condition going on for weeks to months could be due to a reaction of the gland to direct invasion or toxic effects of the ordinary bacteria of the nasopharynx, as maintained by Schilling.[25] Sufficient numbers of cases have been treated with penicillin and sulfadiazine, in doses adequate to control the bacteria of the respiratory tract, without affecting this syndrome, to make it unlikely that these bacteria are the etiological agents. No virus work has been done. Tuberculosis and syphilis are effectively eliminated as etiological agents by the uniform absence of tubercle bacilli and negative serological studies. The entire syndrome and pathological picture seems to suggest an acute inflammatory reaction rather than a degenerative one.

Pathology and Pathogenesis: Grossly, the gland appears to be uniformly involved and to be firm in consistency, grey white or pale brown in color and dense white fibrous strands can be seen traversing the cut surface. The average amount of tissue removed in the bilateral subtotal operations was 24 gm.

On microscopic examination, the following features are apparent:

(1) A dense, young, cellular, connective tissue proliferation circumscribing the lobules and separating them widely.

(2) Destruction and degeneration of thyroid acini with the formation of tubercles containing giant cells which appear to be phagocytosing a central drop of colloid.

(3) A moderately dense inflammatory infiltration of the interstitial tissue by small round cells, mononuclear cells and plasma cells.

(4) A scattered, focal accumulation of fresh and degenerated polymorphonuclear leukocytes found centered in tubercles and in and around degener-

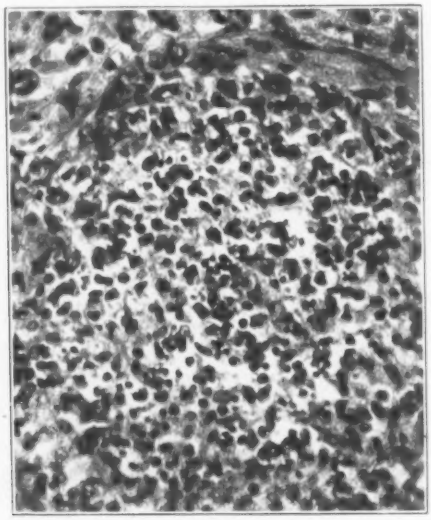

FIG. 1 B.—Subacute Thyroiditis: An area with numerous well preserved and degenerated polymorphonuclear leukocytes (X 322).

ated thyroid acini. This was found in all cases but 1.

(5) Many lobules of thyroid acini which contain colloid and appear to be completely uninvolved.

From these features it is apparent that all parts of the gland are not involved equally or simultaneously. It would seem, then, that the destructive or inflammatory forces do not act at one time, but rather continue to produce changes during the entire course of the disease. It is our belief that the initial inflammatory process begins in the interstitial tissue surrounding those thyroid acini which are at the periphery of the lobule. Monocytes and small round cells infiltrate the follicle wall and lodge in the colloid. Study of serial sections reveals that at some point a breach in the wall is made and the lining epithelium is destroyed. This point serves as a focus for entry of tissue histiocytes which can be seen entering in large numbers from the fibrous tissue. These histiocytes appear singly to phagocytose colloid. In other follicles, the entire lining epithelium is degenerated and desquamated into the center of the follicle and large numbers of histiocytes enter and coalesce to form radially arranged giant cells. These tubercles form a characteristic lesion of the disease. Clusters of polymorphonuclar leukocytes are found inside and around some of the tubercles. No other form of thyroiditis presents a clearly formed tubercle. In the healing stage the colloid disappears from the center of the tubercle and it undergoes fibrous organization.

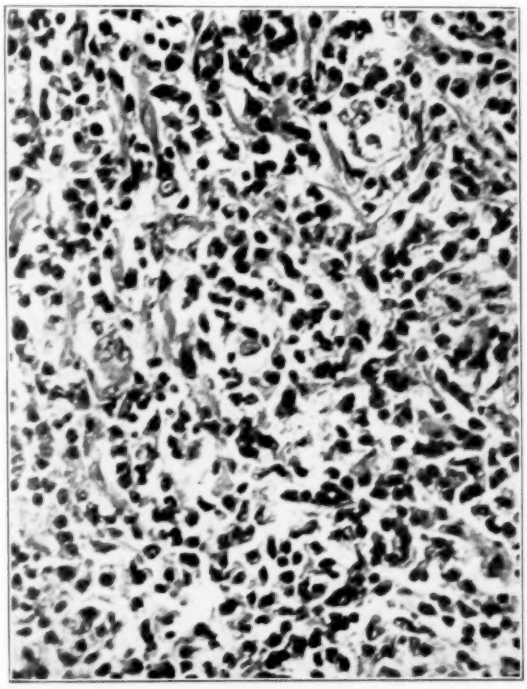

FIG. 2.—Riedel's struma: Plasma cell and lymphocytic infiltration, massive destruction of acini and pronounced increase in collagenous tissue (X 322).

Therapy: The tendency of this disease is toward spontaneous remission. However, the course may be a matter

of months and be quite uncomfortable. The use of thiouracil and Roentgen-rays[3,22] has seemed to shorten the course and these are probably the treatment of choice. Crile[3] reports that 600 to 800 Roentgens to the neck effect a complete remission in a few weeks and that pain and temperature subside in a few days.

CASE C. G., 36 year old white female. *Present Illness:* About 1 month before admission the patient noted increasing nervousness, palpitation, tremor of the hands and marked intolerance to heat. A choking sensation and a swelling of the anterior aspect of the neck were noted. Menses became irregular. She lost about 15 pounds. Two weeks later she began to feel an exquisitely tender swelling of the thyroid and marked pain on swallowing. A persistent diarrhea began and she became febrile with spikes of temperature to 102 daily.

Personal History: Unmarried, no illnesses other than childhood diseases. One sister had a toxic goiter.

Physical Examination: Temperature 101, blood pressure 120/60, pulse 120, respiration 20. The patient was thin and agitated. No ocular signs of hyperthyroidism were present. The trachea was in the midline. The thyroid was visibly enlarged, tender, stony hard and 2 to 3 times normal size. No other unusual physical findings were apparent.

Course: The patient ran a persistent fever of 101 degrees and penicillin 400,000 units daily was given intramuscularly every 3 hours for 1 week. This produced no apparent effect on the process. Lugols 10 mm., 4 times a day was given concomitantly without noticeable effect. The laboratory data showed Kline test negative. Sugar 94 mg. per 100 cc., Total Cholesterol 141 mg., 24% free. Total Protein 8.0 gm.%. Albumin 4.4, Globulin 3.6 gm.%. Blood culture—sterile. Hb 80%, WBC 7,700 (Polys. 68%, Lys. 28, Monos. 1%, Eos. 2, Bas. 1), Urine neg. Sedimentation rate 80 mm./hr. Chest x-ray negative. ECG-sinus tachycardia, right axis deviation. BMR+30% on admission and +16% after 1 week of bed rest. A bilateral subtotal thyroidectomy was performed while the patient was febrile, her postoperative course was smooth and she became afebrile 2 days later.

Operative Findings: A gland, diffusely en-

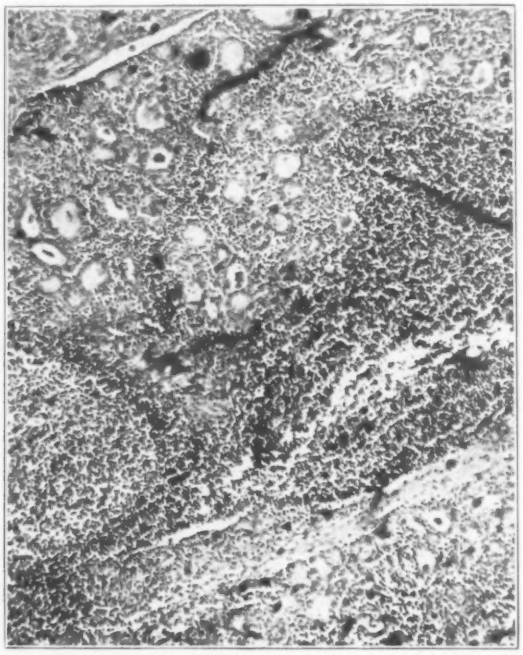

FIG. 3.—Hashimoto's struma: Showing the diffuse nature of the lymphocytic infiltration, the small size of the acini, and the hypertrophy of the lining cells. One large lymph follicle with a germinal center is seen (X 84).

larged to 3 times normal size, very friable, firm and grey white was found. The histopathology is shown in Figure 1.

RIEDEL'S STRUMA (STRUMA FIBROSA). *7 cases. Incidence 0.44%. Clinical Characteristics:* These cases all presented a picture of painless, relatively rapid, bulky, thyroid enlargement. The average duration of symptoms was 1.8 months, varying from 6 weeks to 3½ months. All patients were women, though this is not the usual rule and 2 of Riedel's cases were men. The average was 46 years. Six of the women had had 1 or more pregnancies and 5 of them were beyond the menopause. In only 1 patient did this struma develop on the basis of a pre-existing symptomless goiter. This duration is considerably shorter than other reports,[3,7,16] and may account for the fact that very few of our cases exhibited the severe dyspnea or choking sensations of Riedel's original cases. Only 1 patient complained of difficulty with deglutition and a sensation of tracheal pressure. Two patients were clearly in an early phase of hypofunction, which though not clinically apparent presented itself through low BMR's, low voltage ECG's with isoelectric T waves and an elevated serum cholesterol.

On physical examination, all the glands were described as firm or hard and many felt nodular. Involvement was usually more prominent on one side or another. Laboratory examination except in the hypothyroid cases was noncontributory.

Since these symptoms and signs are not distinctive, the diagnosis is not frequently made preoperatively. Actually the differential diagnosis between this struma and carcinoma is so tenuous, that operation is mandatory.

At operation, the glands were found to be firm, fibrous, avascular, and two were deeply fixed to the surrounding structures. Subtotal thyroidectomies were done in all 7 cases.

Pathology: The average amount of tissue removed was 42 gm. varying from 27 to 56 gm. The specimens appeared to be pale brown or grey, firm and fibrous.

All glands were diffusely involved and approximately to the same degree, though varying widely among each other. The outstanding features were: 1, A dense, diffuse plasma cell and lymphocytic infiltration. 2, Massive destruction of thyroid acini with virtual disappearance of all colloid and an acidophilic swelling and degeneration of acinar epithelium. 3, A pronounced increase in fibrous tissue mainly of a coarse interacinar type. Giant cells were found in several cases but these were not in the form of tubercles and were usually found in the lumina of acini with an intact lining epithelium. There were no clearly distinctive pathological features uniting all cases in this group just as Riedel's original cases were not homogeneous.

Etiology: Jaffe[13] in 1937 reported 4 autopsy cases in which a dense lymphocytic infiltration, a varying degree of fine and coarse fibrosis, absent colloid and desquamation of lining epithelium was noted in the thyroid. The cases were all women who had undergone long and debilitating diseases. He also reviewed cases of Addison's disease and found an associated dense lymphocytic infiltration and fibrosis of the thyroid in 4 of 11 cases. Womach[30] also noted that pathological changes similar to those described by Riedel may be associated with adrenal cortical insufficiency. However, none of our cases exhibited any evidence of a pluriglandular disorder or of a concomitant debilitating disease.

In view of the clinical course it does not seem as though this clinico-pathological picture is the end stage of a process which has first gone through

the stage of what is recognized as struma lymphomatosa. That the processes producing the two syndromes may be basically similar and only different in degree remains a possibility.

Therapy: It is generally agreed that thyroidectomy is the treatment of choice and that only as much tissue should be removed as is necessary to relieve tracheal compression and reduce the bulk of the tumor.

Case I. R., 49 year old white female. *Present Illness:* This patient presented a history of some 3½ months of progressive, painless rapid enlargement of the thyroid with cough, hoarseness and choking sensations. There was no weight loss and none of the signs of hyper or hypothyroid activity were manifested.

Past History: Unmarried, post menopausal for 10 mo. Had been treated for a stomach "ulcer" for 2 years.

Physical Examination: Blood pressure 100/70, pulse 72, temperature 98. The thyroid was diffusely enlarged, 4 times normal size, moderately firm and somewhat nodular. There were no other significant physical findings.

Course: The diagnosis was Riedel's struma. Kline test negative. Blood sugar 74 mg. per 100 cc., Urea 14.8 mg., Cholesterol 311 mg., Hb 59%, WBC 8000 (polys. 69%, lys. 29, Monos. 2), Sedimentation rate 69 mm/hr. ECG low voltage. P-R. interval 0.24 secs. BMR—17%. A subtotal thyroidectomy was done, the post operative course was smooth and uneventful.

Operative Findings: Diffusely enlarged, firm, adherent gland. Right lobe 4½ times normal size. The left lobe was 3 times normal size and extended around the trachea and compressed it.

Pathology: The specimen consisted of 2 portions of thyroid gland weighing 56 gm. The consistency was firm and hard. The cut surface was pale gray-brown.

Microscopic: The acini were small, irregular in shape and were lined by large polygonal cells with a granular eosinophilic cytoplasm and irregularly shaped large, vesicular nuclei. Little colloid was present. Multinucleated giant cells in moderate numbers were seen, but no tubercle formation was present. There was a diffuse, dense infiltration of the parenchyma by small round cells and plasma cells. Large lymph follicles with true germinal centers were seen. There was a marked increase in the interacinar and interlobular connective tissue which was coarse and deeply cosinophilic. Figure 2.

Comment. This case illustrates the massive destruction of functioning thyroid tissue that can occur in this condition in a matter of a few months. Though she did not present symptoms of myxedema, the low voltage ECG, elevated cholesterol and low BMR, indicated the presence of early hypofunction.

Hashimoto's Struma (Struma lymphomatosa) 9 *cases. Incidence* 0.56%. *Clinical Characteristics:* The average age of these patients, all females, was 38 years. The youngest was 6 years of age at the onset of the disease and to our knowledge is the youngest reported case. This case is reported in detail. Joll[14] in his exhaustive study of the subject in 1939 found one case in a child of 10 years. Schilling[25] reported a case in an adolescent female of 15 years of age. At the other end of the scale, Joll's oldest case was 74 years old, but the majority of cases fall in the 3rd to 6th decades. Six of our cases had multiple pregnancies, 3 were post menopausal, 5 were not and the child showed no evidence of endocrine abnormalities. The chief complaint in all cases was a painless, slow-growing enlargement of the thyroid. Duration of this growth ranged from 2 months to 20 years, with a mean duration of 2 years. In 4 cases, nervousness was also recorded as an outstanding symptom. Only 1 case exhibited symptoms of tracheal pressure including hoarseness and dysphagia. Preoperatively, a right recurrent laryngeal palsy was found. This is in contrast to the findings of McSwain and Moore[21] in whose cases pressure symptoms of one type or another were almost uniformly present. No patients were myxedematous preoperatively. Follow-up examinations were obtained in only 1 case, the child, and she showed signs of myxedema and required thyroid extract. It is the general

consensus of all reviewers that about 40 to 60% of these patients will require thyroid extract postoperatively.

Physical examination revealed only a somewhat firm, bilateral thyroid enlargement. Laboratory examinations revealed a serum cholesterol in the high normal range in the 4 cases in which it was performed. Basal metabolic rates were within normal limits, but were done in only 4 cases. Blood counts did not reveal any relative lymphocytosis.

Operative findings consisted of an enlarged, somewhat firm gland. Only 1 gland was noted to be adherent to muscles and this was one to which Roentgen-ray therapy had been given 3 months preoperatively. In 1 other case, the trachea was noted to be angulated and narrowed. A subtotal thyroidectomy was performed in all cases but one in whom a total removal was effected.

Pathology: The amount of tissue removed averaged 57.7 gm. ranging from 11.5 to 138 gm. The tissue appeared firm grey or pale-brown and homogeneous. On microscopic examination, the presence of all the following characteristics were used in selecting cases.

1. Diffuse involvement of the entire gland to the same extent everywhere.
2. A dense infiltration with lymphocytes spread diffusely throughout the parenchyma and also found in focal collections with true germinal centers.
3. A marked swelling of the acinar lining cells in which granular, eosinophilic cytoplasm and large, hypochromatic nuclei are noted.
4. Small acini with slit-like lumina containing almost no colloid.
5. Very little or no increase in fibrous tissue.

Etiology: The only experimental approach was that of McCarrison[19] who claimed to have produced, in rats, a microscopic picture resembling struma lymphomatosa of humans by feeding a diet deficient in vitamins (wheat, meat residue, olive oil and potassium iodide). The work has never been confirmed or expanded. It is interesting to note that the peculiar acidophilic degeneration of the acinar cells resembles closely the changes produced by thiouracil.[1,17,26]

Therapy: Roentgen ray therapy has caused some moderate degree of resolution of the tumor in many cases. However, thyroidectomy appears to be more satisfactory and a conservative removal is indicated.

CASE C. F., 7½ years old white female. *Present Illness:* for 1½ years a progressive swelling of the base of the neck was noticed by the child's mother. There were no associated symptoms of pressure or pain. No personality changes, or heat or cold intolerance, or weight changes were noted.

Past History: The physical and mental development as judged from the age at which the child walked and talked were within normal limits. The child did well in school. Measles, mumps and chicken pox, without sequellae were the only childhood diseases. A tonsillectomy had been performed 1 year before the onset because of recurrent bouts of tonsillitis.

Family History: Hypertension was present in both paternal grandparents. There were no known endocrine disorders. The patient had 2 sisters, 13 years and 5 years of age, in good health.

Physical Examination: Blood preessure 115/85, pulse 96, temperature 100.2. The child was well developed and nourished, alert and cooperative. A firm, somewhat nodular mass was present in the neck attached to the trachea. There were no other physical findings of significance.

Course in Hospital: The clinical diagnosis was a nontoxic nodular goiter. Hb 77%, WBC 10,400 (polys. 79%, lys. 16, Monos 5). A subtotal thyroidectomy was performed. The postoperative course was uneventful. About 3 months after the operation, the child began to gain weight rapidly, her eyelids became edematous and the BMR was found to be −20%. Thyroid, ½ gr. daily was given with complete remission of symptoms. Eight months after the operation, x-rays of wrists, elbows and knees showed normally developed epiphyses, Cholesterol was 233 mg. per 100 cc. and BMR−8%. The child was admitted to the hospital for re-evaluation 1½ years later. She had been maintained on thyroid extract during that period, with normal growth and

mental development. Her laboratory work up showed a cholesterol of 204 mg., calcium 10.8 mg., phosphorus 5.3 mg., and alkaline phosphatase 8.0 units, BMR—17%.

Pathology: The specimen consisted of 2 portions of thyroid tissue weighing 22 gm. The cut section was pale, tan, homogeneous and meaty in consistency. On microscopic examination, the gland appeared to be uniformly involved, and diffusely infiltrated by lymphocytes. Numerous germinal centers were present, acini were small, round and contained little colloid. Acinar cells were low to high cuboidal showing a typical acidophilic degeneration. There was no increase in fibrous tissue. Figure 3.

Summary. A total of 1,595 thyroidectomies performed since 1940 has been reviewed and 24 cases of nonspecific thyroiditis were selected for analysis.

Eight cases formed a closely knit clinical and pathological entity characterized clinically by painful, febrile, rapid enlargement of the thyroid with a high incidence of symptoms of tracheal pressure and pathologically by the finding of numerous tubercles and giant cells but no tubercle bacilli; presence of dense fibrous connective tissues and presence of polymorphonuclear leukocytes in clusters within the tubercles. This is the subacute, pseudotuberculous thyroiditis group.

Seven cases corresponded rather closely to the original Riedel's struma and were so classified. Painless, relatively rapid, extraordinary firm thyroid enlargement was the clinical aspect and a pronounced diffuse fibrosis and lymphocyte and plasma cell infiltration were the pathological findings.

Nine cases of struma lymphomatosa were reviewed and so classified on the basis of a slow, large, painless thyroid growth displaying on microscopic examination a diffuse infiltration by lymphocytes with numerous follicles containing germinal centers, acidophilic degeneration of acinar cells and little increase in fibrous tissue. The youngest case on record in a child of six was reported.

The similarities and differences between the various groups was discussed and the literature reviewed.

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SOME ASPECTS OF HYPERTENSIVE DISEASE OF PREGNANCY TREATED BY SPLANCHNICECTOMY*

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IT IS definitely established that the existence of arterial hypertension before or during a pregnancy constitutes a complication of dangerous potentialities to the pregnancy. Also, the onset of hypertension during pregnancy all too frequently results in persistent hypertension for the mother. Our interest has been in hypertensive disease in general, and particularly in the surgical treatment of this disease. But problems of pregnancy in varied aspects have frequently confronted us in our management of hypertensive females by splanchnicectomy. It thus appeared advisable to investigate the relationship of the operation of splanchnicectomy to hypertensive disease of pregnancy.

Since November 1933 more than 2000 hypertensive patients have been treated at the University Hospital with the surgical procedure of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy. Half of them were females. Thirty-seven per cent of these women were less than 40 years old at the time of operation and thus were in the childbearing age; 28 of them became pregnant after operation, with and without our counsel. The results of 34 pregnancies in these 28 splanchnicectomized patients are reported here.

During the past 5 years splanchnicectomy was performed during the second trimester of pregnancy in 5 additional cases, each suffering from severe toxemia superimposed upon prepregnant hypertension. This is a new therapeutic approach to a serious and vexing specialized problem.

Many observers[1,5,13,14] have postulated that hypertension of pregnancy is merely an accentuation of a frank or latent hypertension which existed prior to pregnancy, and some believe that a toxemic pregnancy does not injure normal vascular and renal systems. There is no unity of opinion concerning this important matter. It also has been generally assumed that females whose hypertension originates during pregnancy do not differ clinically from females whose hypertension is in no way related to pregnancy. In order to uncover information which might help clarify the foregoing, 452 females who were operated upon during the years 1934 through 1942 inclusive, and who have thus been followed from 5 to 13 years, were divided into 2 groups depending upon whether or not their hypertension was first discovered during a pregnancy. The 2 groups have been compared as to the extent of their hypertensive disease and as to the end-results from splanchnicectomy.

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Pregnancy Subsequent to Splanchnicectomy. The hypertensive female who becomes pregnant is not likely to go through childbearing successfully. In the first place, she is markedly vulnerable to a toxemic pregnancy. Dexter and Weiss[2] followed 39 prepregnant hypertensives through pregnancy, and toxemia occurred in half of them.

Secondly, a toxemic pregnancy may permanently harm the mother. In the Dexter and Weiss series, approximately one quarter of those who developed toxemia manifested higher blood pressure levels and more extensive hypertensive disease after the pathological pregnancy than before. Reid and Teel[13] followed 122 patients with known essential hypertension prior to pregnancy, and at a late postpartum examination, 44% of them showed higher blood pressure levels than when first seen.

Thirdly, the fetal prognosis is discouraging for prepregnant hypertensives. Hypertension in the mother definitely interferes with the well-being of the fetus. Dieckmann and Brown[4] found a 21% fetal mortality in mothers who had essential hypertension. For the 122 patients in the series of Reid and Teel[13] the fetal mortality was 21.9%. It is thus seen that pregnancy in an already hypertensive female is likely to have a disappointing, and sometimes tragic, ending.

We have followed 28 hypertensive females who were first treated by splanchnicectomy and who subsequently experienced pregnancies; the data for each case are given in Table 1. Naturally, they were relatively young at the time of the operation, their average age being 28 years. The average duration of hypertension from the time of its discovery until operation was 4.2 years. The average preöperative blood pressure was 208 systolic, and 135 diastolic.

Angiospastic retinitis was present prior to operation in 21 of the 28. Two cases had severe neuroretinitis with papilledema.

When these 28 patients were classified according to our preöperative clinical classification of arterial hypertension,[10] 10 cases were in group three, in which organic heart disease is predominant, the diagnosis being confirmed by either a definitely abnormal electrocardiogram or a teleoroentgenogram showing cardiac enlargement or both. Five patients were in group five, cases in which impaired renal function is predominant. It is thus seen that hypertensive disease was already well-established in these 28 females before splanchnicectomy.

The average time interval between operation and the subsequent pregnancy was 2.6 years, and the average blood pressure level prior to pregnancy was 144 systolic and 94 diastolic, for all 28 cases.

Results. Eighteen cases began pregnancy with normal blood pressures as a result of splanchnicectomy. Seventeen of these females gave birth to 18 normal, living infants.

But on the other hand, of 10 women who started pregnancies with blood pressure levels above normal (greater than 150/90), only 2 delivered living infants at term. Case 10 began pregnancy with a blood pressure of 152/108, and Case 24 entered pregnancy with a blood pressure of 210/130; in each instance the hypertensive state was uninfluenced by the pregnancy. The remaining 8 women who began pregnancy with elevated blood pressure levels no matter how slight, either had to be interrupted or gave birth to stillborn fetuses.

No patient whose blood pressure was within normal range prior to pregnancy developed a toxemia of pregnancy. Without such a good result from splanchnicectomy, the expected incidence of toxemia would have been

TABLE 1.--CLINICAL DATA ON 28 HYPERTENSIVE FEMALES WHO EXPERIENCED PREGNANCIES SUBSEQUENT TO SPLANCHNICECTOMY

Case No.	Preoperative Status							Blood Pressure Level Prior to Pregnancy	Time (Years) Between Operation and Onset of Subsequent Pregnancy	Condition Through Pregnancy				Condition of Infant	Findings at Recent Exam.		
	Age	Duration of Hypert in Yrs.	Blood Pressure	Symptoms	Fundus K.C.W. Group	Clinical Classif.	Year of Operation			Blood Pressure Range	Albumin Uria	Edema	Symptoms		Time Interval Since Delivery in Years	Blood Pressure	Symp. toms
1	38	6	232/140	Severe	3	II	1935	140/90	1.8	130-140/100-110	0	0	0	N	10.1	141/96	0
2	23	1	270/138	Mod.	3	III	1935	150/87	3.0	130-170/100-112	++	0	+	N	8.7	158/102	0
3	33	2	202/112	Mod.	3	III	1935	138/90	4.1	140-172/90-110	0	0	0	N	7.0	165/100	
4	16	1.5	178/110	Mild	3	II	1936	120/78	4.2	120-170/80-88	0	0	0	Interrupted NVF*	2.7	120/80	0
								132/74	6.3	136-168/74-90	0	0	0	Interrupted NVF			
								130/84	7.5	132-160/80-92	0	0	0	Interrupted NVF			
5	28	1	242/158	Severe	3	III	1937	124/86	1.4	112-128/84-90	0	0	0	N	7.6	124/68	0
6	23	2.5	220/140	Severe	3	II	1938	126/82	4.4	120-126/82-88	0	0	0	N	0.6	112/78	0
								120/86	8.0	114-128/80-90	0	0	0	N			
7	32	5	200/140	Severe	2	V	1938	124/90	4.1	135-148/88-96	0	0	0	N	4.0	135/86	0
8	28	2	210/120	Mod.	3	II	1939	132/86	1.8	120-170/70-110	0	0	0	N	5.2	160/105	0
9	26	4	163/106	Mod.	2	II	1940	135/84	2.2	116-140/76-85	0	0	0	N	2.0	125/80	0
10	30	6	200/150	Mod.	2	III	1940	152/108	3.2	150-176/108-120	0	0	0	N	2.8	148/105	0
11	20	2	160/104	Mild	2	II	1940	105/72	6.4	110-136/70-82	0	0	0	N	0.2	132/80	0
12	22	3	165/110	Mod.	1	V	1941	128/86	4.3	110-134/64-80	0	0	0	N	0.9	138/84	0
			220/					150/	1.6	148-170/	++	0	0	Erythroblastosis			

13	27	2	220/170	Mod.	3	II	1941	150/100 150/105	1.6 6.1	148-170/80-110 150-160/105-110	++ 0	0 0	0 0	Erythroblastosis Spontaneous Abortion	1.0	150/105	0
14	34	12	212/106	Mod.	2	II	1942	144/94	2.4	160-220/100-110	+	0	0	Interrupted NVF*	2.5	168/104	0
15	24	3	224/160	Severe	4	VI	1942	120/80	4.7	118-180/60-85	0	0	0	N	0.2	140/82	0
16	33	7	240/144	Severe	3	V	1942	206/135	2.8	220-245/140-150	0	0	0	Interrupted NVF*	2.0	226/126	+++
17	31	0.5	195/135	Mod.	3	II	1942	132/90	0.4	114-130/80-90	0	0	0	N	3.8	126/86	0
18	39	3	200/120	Mod.	3	III	1942	190/110	2.3	195-225/110-120	+	0	0	Interrupted NVF*	2.1	200/110	++
19	28	8	196/115	Mod.	3	II	1942	114/78	3.8	108-132/70-84	0	0	0	N	0.8	122/80	0
20	21	1.5	200/150	Severe	3	III	1943	164/120	3.4	226-250/150-170	++	++	++++	Interrupted Stillborn	0.2	200/140	++
21	28	8	200/130	Mild	3	III	1943	135/85	1.5	132-160/78-104	+	0	0	N	2.2	142/90	0
22	28	4	255/162	Severe	4	VI	1943	175/110	0.3	180-260/120-155	++	++	++	Interrupted Stillborn	3.0	148/104	0
23	27	1.5	203/144	Mod.	3	II	1943	142/80	2.0	130-154/76-94	0	0	0	N	1.1	138/84	0
24	24	8	206/132	Mod.	3	V	1944	165/112 150/100	1.5 2.7	165-200/115-130 155-185/106-115	++ ++	++ ++	++ ++	Stillborn Interrupted NVF*	1.6	150/102	0
25	37	10	240/154	Severe	3	V	1944	180/125 210/130	1.9 2.7	195-220/130-135 220-240/130-135	0 0	+ +	0 0	Stillborn Prolapse of Cord N	0.2	230/130	0
26	27	8	223/135	Severe	3	III	1944	140/76	2.2	135-150/74-85	0	0	0	N	0.6	146/80	0
27	30	1.5	196/138	Severe	3	III	1944	108/74	1.3	112-128/60-80	0	0	0	N	1.0	115/76	0
28	29	4	234/142	Severe	3	III	1944	166/95	0.6	160-188/90-130	++	+	0	Stillborn	1.8	130/90	0
Aver-age	28	4.2	208/135					144/94	2.6	144-172/90-107					2.7	148/91	

*NVF - Non-viable fetus.

50%; and the 10 splanchnicectomized females who began 14 pregnancies with elevated blood pressure levels did show exactly a 50% incidence of toxemia.

Twelve cases maintained blood pressure levels entirely within normal limits throughout 13 full-term pregnancies; one case maintained normal blood pressure throughout 2 pregnancies subsequent to splanchnicectomy. Mild to moderate elevations of blood pressure occurred in 14 pregnancies, in 5 of which living infants were delivered at term. In only 4 cases did the blood pressure during pregnancy reach or exceed the pre-splanchnicectomy level; each was interrupted.

Each of these 28 females who had pregnancies subsequent to splanchnicectomy have been examined recently. The time interval between the examination and the previous delivery averaged 2.7 years. Blood pressure levels were being maintained within normal limits (150/90 or less) in 15 cases, or 53.6%. Prior to splanchnicectomy the blood pressure levels of these 15 patients averaged 200/126.

In 9 patients the recent examination revealed mildly elevated blood pressure levels in the range of 150 to 170 systolic, and 105 diastolic. Prior to operation the average blood pressure in these 9 cases was 233/137. Only 4 cases recently showed blood pressure levels greater than 170/105.

It is readily apparent that it is inadvisable for the hypertensive female who does not obtain a good result from splanchnicectomy to hazard a pregnancy, for her chances of obtaining a living infant are meager. On the other hand, the once hypertensive female who maintains a normal blood pressure following splanchnicectomy, can be assured that if she does become pregnant, her chances are excellent for delivery of a living infant, and that she has probably been protected against any related vascular damage. In this group of splanchnicectomized females, pregnancy following operation resulted in no harmful hypertensive complications.

The experiences of Newell and Smithwick[7] confirm the foregoing. They have reported the results in 14 hypertensive females who were treated by lumbodorsal splanchnicectomy and who then had a subsequent pregnancy, except for 1 case in which operation was performed during the first trimester. Thirteen infants were living and well. Only 1 pregnancy had to be interrupted. Six weeks postpartum, the average blood pressure of the series was 133/87.

Splanchnicectomy Performed During Pregnancy. A toxemia superimposed upon prepregnant hypertension presents a discouraging problem. Almost always the only recourse is interruption of the pregnancy. A new approach to this specialized problem has been tried at the University Hospital during the past 5 years. The operation of bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy has been performed during the second trimester in 5 such cases which have been reported in detail[12].

This surgical treatment is aimed directly at the underlying hypertensive disease, for it is felt that the complicating toxemia is a consequence of the pre-existing hypertensive state.

In 2 cases, the results have been excellent; following operation in both, the toxemia disappeared, normal blood pressure levels were achieved, living infants were obtained, and normal blood pressures have persisted for 4 years and 2 years respectively since delivery.

In the remaining 3 cases the operation exerted no influence on the toxemia, but in 1 of the cases the blood pressure levels since delivery have been significantly decreased as compared to the prepregnant levels.

Hypertension Having Its Onset During Pregnancy Differentiated from Hypertension With Onset Without Relation to Pregnancy. The 452 hypertensive females who were operated upon during the years 1934 through 1942 inclusive have been divided into 2 groups depending upon whether or not their hypertension was first recognized during pregnancy. In 100 of them, elevated blood pressure was first noted at the time of a pregnancy; it is indeed likely that some of these cases may have had unrecognized high blood pressure prior to pregnancy, but since there is no way of determining this, it is impossible to correct for this unknown factor. In the remaining 352 females in this series, onset of hypertension had no relation to pregnancy.

The clinical picture of the hypertensive state of one group differs in certain respects from that of the other, but it cannot be stated that the degree of hypertensive involvement in one group is greater or more serious than that of the other. Diastolic blood pressure levels prior to operation were higher in the group related to pregnancy; also organic heart disease was predominant in a greater percentage of the cases in this group than in the other. But the incidence of cerebrovascular accidents and malignant hypertension prior to operation was greater in the group whose disease did not have its onset in pregnancy. There was no significant difference as to age at time of operation or as to known duration of hypertension prior to operation.

Even though there was no remarkable clinical difference in the hypertensive state of the 2 groups, yet they

TABLE 2.—SURVIVAL TABLE AFTER SPLANCHNICECTOMY FOR 89 FEMALES WHOSE HYPERTENSION BEGAN DURING PREGNANCY, EXCLUDING 11 CASES OF MALIGNANT HYPERTENSION

Years of Operation	Number of Cases	Percentage Alive								
		5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 years
1934	1	100	100	100	100	100	100	100	100	100
1935	10	100	100	90.0	90.0	80.0	80.0	80.0	70.0	
1936	7	71.4	71.4	71.4	57.1	42.9	42.9	42.9		
1937	12	91.7	91.7	91.7	83.3	83.3	83.3			
1938	12	75.0	66.7	58.3	58.3	58.3				
1939	7	85.7	85.7	85.7	57.1					
1940	9	88.9	77.8	77.8						
1941	12	91.7	91.7							
1942	19	100.0								

TABLE 3.—SURVIVAL TABLE AFTER SPLANCHNICECTOMY FOR 291 FEMALES WHOSE HYPERTENSION HAD NO RELATION TO PREGNANCY, EXCLUDING CASES OF MALIGNANT HYPERTENSION

Years of Operation	Number of Cases	Percentage Alive								
		5 years	6 years	7 years	8 years	9 years	10 years	11 years	12 years	13 years
1934	8	87.5	62.5	62.5	62.5	62.5	50.0	37.5	37.5	37.5
1935	22	86.4	81.8	81.8	81.8	77.3	72.7	68.2	63.7	
1936	21	81.0	81.0	71.4	66.7	62.0	62.0	57.3		
1937	30	83.3	83.3	83.3	76.7	70.0	70.0			
1938	35	82.9	82.9	82.9	80.0	80.0				
1939	30	90.0	90.0	90.0	90.0					
1940	29	96.6	96.6	96.6						
1941	44	88.6	81.8							
1942	72	81.9								

significantly differ in their overall response to splanchnicectomy. Both groups responded well to the operation, but the end-results are definitely better for the females whose hypertensive disease had its origin during a pregnancy. The postpartum-persistent-hypertensives show better survival rates and maintain lower blood pressure levels after splanchnicectomy.

The survival tables (Tables 2 and 3) for both groups are remarkably good, and it is surprising that the survival rate among the females whose hypertension is related to pregnancy should be even better than that of the other females. In the former group of 89 hypertensive women (excluding 11 cases of malignant hypertension), 90% survived 5 years after operation; for the 29 cases operated upon 11 to 14 years ago, the 10-year survival rate was 76%. While for the second group of females with onset of hypertension bearing no relation to pregnancy, the 5-year survival rate was 86%, and the 10-year survival rate was 65.4%.

Post-splanchnicectomy survival among malignant hypertensives whose elevated blood pressures were first discovered during pregnancy does not differ significantly from malignant hypertensives whose disease bears no relation to pregnancy. The cases of malignant hypertension have been dealt with separately from the other cases of essential hypertension in the computing of the foregoing survival statistics since the malignant type evidently represents a separable, fulminating phase of the disease. Our diagnostic criteria[11] for malignant hypertension are: (1) a rapidly-progressive, deteriorating, clinical course of recent onset; (2) severe neuroretinitis with definite papilledema of 1 diopter or more; (3) high diastolic blood pressure; and (4) evidences of constitutional involvement.

The group of females whose hypertensive state was related to pregnancy has maintained a better blood pressure response to splanchnicectomy than the other group of female hypertensives, even though the response of the latter also has been good. Among the former group, 23% were maintaining normal blood pressure levels (150/90 and less) 5 to 13 years since operation, and in another 22% the blood pressure was markedly reduced by 80 mm. systolic and 25 mm. diastolic or more as compared to the preöperative level (Table 4). In the latter group, 15.4% were maintaining normal blood pressure levels, and another 13.6% showed marked reduction 5 years or more after operation.

TABLE 4.—BLOOD PRESSURE RESPONSE IN 452 FEMALES, 5 TO 13 YEARS AFTER SPLANCHNICECTOMY, INCLUDING CASES OF MALIGNANT HYPERTENSION

	Number of Cases	Now Normal	Marked Reduction (Of 80 mm. Systolic & 25 mm. Diastolic or More)	Significant Reduction (Of 40 mm. Systolic & 25 mm. Diastolic or More))	No Significant Change	Alive But No Recent B.P. Worse	Determination	Dead
Onset During Pregnancy	100	23 (23%)	22 (22%)	19 (19%)	4 (4%)	0	5 (5%)	27 (27%)
No Relation To Pregnancy	352	54 (15.4%)	48 (13.6%)	70 (20%)	32 (9%)	5 (1.5%)	35 (10%)	108 (30.5%)

The Problem of Post-Toxemic Hypertension. In large series of pregnancies, Stander[15] found an 8.4% incidence of toxemia, Dieckmann[3] a 6.7%, and

Page[8] a 9% incidence. Thus toxemia occurs in about 8% of all pregnancies.

Dieckmann and Brown[5] reviewed the literature and concluded that approximately one quarter of the patients with pre-eclampsia and eclampsia develop permanent hypertensive disease after pregnancy. Herrick and Tillman[6] also found that 25% of women who have had a toxemic pregnancy, are left with permanent postpartum vascular disease. Peckham[9] reported a much higher incidence (63.4%) of chronic vascular damage as the late result in 500 cases of toxemia of pregnancy. Reid and Teel[13] were very careful in determining that both the prepregnant blood pressure and urine were normal in a series of 235 patients who later developed mild pre-eclampsia; 21% had sustained hypertension 6 months to 3 years postpartum. Simrall[14] followed 91 patients who developed toxemia during pregnancy and who definitely had normal blood pressure levels prior to pregnancy or during the first trimester; at a late postpartum examination he found that 30% manifested abnormally elevated blood pressure.

Since roughly 25% of females who have had a toxemic pregnancy are left with permanent postpartum hypertension, and since toxemia occurs in about 8% of pregnancies, then about 2% of all women who become pregnant may be expected to develop permanent hypertension as a result of pregnancy.

There were 3,440,000 births in this country in 1946. The stillbirth rate was 27 per 1,000 live births. Of the 3,500,000 women who went through pregnancies in the single year of 1946, possibly 70,000 now have permanent hypertensive disease. The problem of post-toxemic hypertension is thus one of considerable magnitude; it is also serious enough to warrant thought and action by the physicians responsible for the welfare of these women.

These females who are now hypertensive as a result of pregnancy constitute a group in whom excellent results can be expected from splanchnicectomy. Five to 13 years after operation one quarter of this group can be expected to be maintaining normal blood pressure levels. The operative risk is minimal, providing the disease has not yet progressed to its malignant phase. The operative mortality for all females, excluding cases of malignant hypertension, is 0.5%. For females with malignant hypertension, the operative mortality is 7.7%.

At the present time the operation of splanchnicectomy represents an effective therapeutic approach to hypertensive disease, and it is especially efficacious in coping with the problem of post-toxemic hypertension. This operation must be considered for the female whose blood pressure persists at hypertensive levels for more than one year following childbirth.

Summary and Conclusions. 1. The large number of female hypertensives who were treated with bilateral supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy at the University of Michigan Hospital afforded an opportunity to study several aspects of hypertensive disease of pregnancy.

2. Twenty-eight hypertensive females who were treated by splanchnicectomy, subsequently experienced 34 pregnancies. Of 18 cases who began pregnancy with normal blood pressures, 17 gave birth to 18 infants, and 15 were still maintaining normal blood pressure levels at a recent examination, averaging 2.7 years since delivery and 6.3 years since operation. On the other hand, of 10 cases who started pregnancies with blood pressure levels above 150/90, only 2 delivered living infants at term.

3. Not one of 18 cases who responded to splanchnicectomy by maintaining

normal blood pressure levels after operation and who subsequently became pregnant developed a toxemia of pregnancy.

4. No splanchnicectomized female suffered any late, harmful vascular effects as the result of pregnancy.

5. Five cases of toxemia superimposed upon prepregnant hypertension have been treated by splanchnicectomy performed during the second trimester of pregnancy, and in 2 cases the results have been excellent. Following operation in both, the toxemias disappeared and normal blood pressure levels were achieved for the remainder of the pregnancies and during a long postpartum follow-up period.

6. When female hypertensives are divided into 2 groups depending upon whether or not their hypertension had its origin during a pregnancy, there is little variance in their disease pictures, but there is significant difference in their overall response to splanchnicectomy. Both groups respond well to the operation, but the end-results are definitely better for the females whose hypertensive state began in a pregnancy.

7. The young hypertensive female who wishes to have children should first have the essential hypertension treated by splanchnicectomy. If she maintains normal blood pressure levels for 1 year after operation, she may with reasonable safety become pregnant and with the assurance that her chances are excellent for giving birth to a normal infant.

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THE SECRETORY RESPONSE TO HISTAMINE IN INDIVIDUALS WITH A NORMAL AND ABNORMAL GASTRIC MUCOSA

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Although numerous studies have been made of the clinical and gastroscopic aspects of gastritis,[2] to our knowledge, a definitive correlation of the appearance of the gastric mucosa with its secretory capacity has not been made. The purpose of the present paper is to report such an analysis.

A study was made of 250 patients in whom the physical and laboratory examinations were normal and in whom complete roentgen studies of the gastro-intestinal tract were negative.

These cases were divided into 4 groups: (a) 100 with a gastroscopically normal mucosa; (b) 50 with atrophy, as evidenced by grayness of the mucosa and visible capillaries ("atrophic gastritis"); (c) 50 with inflammatory changes in the mucosa, including edema, erythema and exudate ("chronic superficial gastritis"); and (d) 50 cases with an irregular cobblestone-like mucosa, ("chronic hypertrophic gastritis"). Gastric acidity was measured by the histamine test using 0.1 mg. of histamine hydrochloride per 10 kg. body weight; fractional specimens were obtained every 10 minutes for 1 hour; the values are expressed as clinical units of the maximum free acidity in any specimen.

TABLE 1.–CORRELATION BETWEEN GASTROSCOPIC APPEARANCE OF THE MUCOSA AND HISTAMINE-STIMULATED SECRETION

Maximum Free Acidity (Clinical Units)	Normal Mucosa (100 pats.)	Atrophy* (50 pats.) per cent	Inflammatory** Changes (50 pats.) per cent	Cobblestone-like Mucosa*** (50 pats.) per cent.
Achlorhydria	5	30	30	2
1-20 units	1	10	6	2
21-40 units	5	2	18	10
41-60 units	18	16	14	12
61-80 units	20	16	6	26
81-100 units	22	10	14	22
More than 100	29	16	12	26
Total (per cent)	100	100	100	100

* "Atrophic gastritis"
** Erythema, edema, exudate ("superficial gastritis")
*** "Hypertrophic gastritis"

Results and Discussion. The findings are listed in Table I.

Among the 50 patients with atrophy, there were 15 with histamine achlorhydria. The degree of atrophy in this subgroup is indicated in Table 2. It is of

TABLE 2.–TYPES OF ATROPHY IN HISTAMINE ACHLORHYDRIA

Type		No. Patients
Patchy atrophy		3
Generalized atrophy		12
Slight	0	
Moderate	3	
Severe	9	
Total		15

interest that the maximum free acidity exceeded 40 clinical units and rose as high as 126 units in 29 of the 50 patients with atrophic changes. The type of atrophy in this subgroup is shown in Table 3. Except for this observation,

TABLE 3.–TYPES OF ATROPHY IN PATIENTS WITH ACIDITIES ABOVE 40 CLINICAL UNITS

Type		No. Patients
Patchy atrophy		8
Generalized atrophy		21
Slight	7	
Moderate	10	
Severe	4	
Total		29

there was no significant correlation between the level of free acid and the gastroscopic appearance of the gastric mucosa in this series of patients.

It is apparent that atrophic, inflammatory, or hyperplastic changes of the mucosa do not necessarily alter the secretory response to histamine stimulation. This finding is in agreement with that of Schindler *et al.*,[3] who, in a study of 82 cases of spontaneous histamine achlorhydria, observed various types of gastritis as well as a normal mucosa. The present data, in accord with the observations of Schindler, demonstrate that the most common anatomic basis for anacidity is diffuse inflammation and atrophy. The incidence of anacidity in patients with inflammatory and with atrophic changes was 30%, in contrast to 5 and 2%, respectively, for individuals with a normal mucosa and for patients with hyperplastic alterations.

Inflammatory changes with achlorhydria suggest involvement of the acid-secreting cells deep in the pits of the glands and not a mere "superficial gastritis". In a previous study of achlorhydria produced by roentgen irradiation,[1] it became evident histologically that the edema, erythema and exudate of the mucosa, as seen gastroscopically, were not limited to the superficial layers of the stomach but involved both the mucosa and submucosa. Such anatomical differences probably explain the variability of gastric secretion in patients with gastritis.

It is interesting that of the 50 patients with definite atrophy, 29 were able to secrete gastric juice with a free acidity above 40 clinical units. In 21 of these, the atrophy was diffuse and in 4 it appeared to be extremely severe. This finding indicates that numerous, well functioning, acid-secreting cells may be present, even though the atrophy as seen gastroscopically may seem to be pronounced.

Conclusions. 1. The correlation between the maximum free acidity and the gastroscopic appearance of the gastric mucosa is not exact.

2. Achlorhydria may occur with a normal mucosa, as well as with various types of gastroscopic alterations. However, in the present study, achlorhydria was observed in only 5% of individuals with a normal mucosa and in only 2% of those with a cobble-stone (hypertrophic) mucosa, as compared with an incidence of 30% each in patients with atrophy (atrophic gastritis) and with inflammatory changes (superficial gastritis).

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THE GASTROSCOPIC APPEARANCE OF THE GASTRIC MUCOSA IN PEPTIC ULCER

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Recent studies have demonstrated significant differences in the maximum free acidity of the gastric secretion between patients with gastric and those with duodenal ulcer. The maximum free acidity after histamine was low in 21% of the gastric ulcer group, whereas in duodenal ulcer it uniformly exceeded 50 clinical units.[10] The output of acid in the 12 hour night secretion averaged 273 mg. in gastric ulcer, 661 mg. in a series of normal individuals, and 2242 mg. in the duodenal ulcer.[6] A comparison of the maximum free acidity and the gastroscopic findings in individuals without demonstrable organic disease of the gastrointestinal tract indicated no exact relationship.[9] However, achlorhydria was noted in 30% both of patients with atrophic and of those with "superficial" inflammatory changes, in contrast to an incidence of 5% among individuals with a normal gastric mucosa and 2% among those with hypertrophic changes.

The present study was undertaken: a) to compare similarly the gastric acidity and the gastroscopic findings in patients with gastric ulcer and with duodenal ulcer, and, b) to seek a possible explanation for the pronounced difference in gastric secretion between the two ulcer groups.

Present Study. Two consecutive series of patients with duodenal and gastric ulcer were collected; individuals with gastroenterostomy, gastric resection, or vagotomy were not included. Gastric acidity was measured by the histamine test (0.1 mg. per 10 kg. body weight) and expressed in clinical units of the maximum free acidity as determined during the conventional one hour procedure.

The gastroscopic findings were classified as: a) normal, b) atrophy (so-called "atrophic gastritis"), c) an irregular cobblestone-like mucosa (so-called "hypertrophic gastritis"), and d) edema, hyperemia, and adherent exudate (so-called "superficial gastritis"). The presence of erosions and hemorrhagic areas was noted in groups b, c and d, but not considered in this study.

Gastric Ulcer. Among 150 consecutive cases of benign gastric ulcer the gastric mucosa distant from the ulcer appeared normal in 45% and abnormal in 55% (Table 1).

Table 1.—Gastroscopic Appearance of the Gastric Mucosa in Gastric Ulcer
(150 Cases)

Mucosa	No. Cases	Per cent
Normal	67	45
Edema, erythema, exudate	16	10
Hyperplastic features	28	19
Atrophy	39	26
Total	150	100

The correlation between the gastroscopic changes and the maximum free acidity is expressed in Table 2.

TABLE 2.–CORRELATION BETWEEN APPEARANCE OF THE MUCOSA AND MAXIMUM FREE ACIDITY IN GASTRIC ULCER
(120 Cases)

Maximum Free Acidity (Histamine) Clinical Units	Normal	Atrophy	Hyperplastic Features	Edema, Erythema, Exudate
		Per cent of Cases		
1-20	7	30	4	26
21-40	8	10	10	12
41-60	16	20	21	12
61-80	16	26	20	19
81-100	32	10	22	12
More than 100	21	4	23	19
Total	100	100	100	100

Duodenal Ulcer. One hundred consecutive cases of duodenal ulcer had one or more gastroscopic examinations. The mucosa consistently appeared normal in 47% and abnormal in 53% (Table 3). In these 100 cases erosions were observed in 11 and a benign polyp in one patient.

TABLE 3.–GASTROSCOPIC APPEARANCE OF THE GASTRIC MUCOSA IN DUODENAL ULCER
(100 Cases)

Mucosa	No. Cases
Normal	47
Edema, erythema, exudate	7
Hyperplastic features	41
Atrophy	5
Total	100

The gastroscopic findings and the maximum free acidity are correlated in Table 4.

Discussion. The present analysis again demonstrates that peptic ulceration may occur with any type of gastric mucosa, the only essential being the presence of free hydrochloric acid. Previous gastroscopic studies[2-4,7,11-14] in patients with duodenal ulcer have yielded varying figures both for the incidence and the type of gastritis. The present study, however, indicates a considerable difference between gastric and duodenal ulcer in the appearance of the gastric mucosa. Thus, a cobblestone-like mucosa was noted in 41% of patients with duodenal ulcer and in only 19% of cases with gastric ulcer. Perhaps of greater significance is the fact that atrophy was recorded in only 5% of cases with duodenal ulcer in contrast to 26% of those with gastric ulcer. Among 18 patients with gastric ulcer and a low free acidity, inflammatory changes (edema, erythema, exudate) or diffuse atrophy were observed in 13. Of particular interest in this regard are the observations of Meyers[8] who, in a recent study, noted that the

TABLE 4.–CORRELATION BETWEEN APPEARANCE OF THE MUCOSA AND MAXIMUM FREE ACIDITY IN DUODENAL ULCER

Maximum Free Acidity (Histamine) Clinical Units	Normal	Atrophy	Hyperplastic Features	Edema, Erythema, Exudate
		Per cent of total number of Cases		
1-20	--	..	--	..
21-40	--	..	--	..
41-60	1	1	2	1
61-80	6	2	9	1
81-100	14	..	9	1
More than 100	26	2	21	4
Total	47	5	41	7

number of parietal cells per high power field in the gastric fundus of patients with gastric ulcer varied from 0 to 40, whereas in duodenal ulcer the cell counts ranged from 60 to 90. The incidence of atrophic changes in gastric ulcer has been reported previously as 13%,[5] 6%,[13] and zero[7]; Baker[1] records an incidence of 60%.

This difference in the appearance of the gastric mucosa between duodenal and gastric ulcer coincides in many cases with the pronounced difference in gastric secretion observed in these two groups.

Conclusions. 1. The gastric mucosa in duodenal and in gastric ulcer gastroscopically may appear normal, atrophic, hyperplastic or present inflammatory changes—erythema, edema, and exudate.

2. The incidence of atrophy of the gastric mucosa is considerably higher in gastric than in duodenal ulcer, whereas the incidence of a hyperplastic mucosa is considerably higher in duodenal than in gastric ulcer.

3. The frequency of atrophic and inflammatory changes of the gastric mucosa in gastric ulcer accounts in the majority of the cases for the low output of acid.

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DIABETES AND VASCULAR DISEASE IN YOUTH*

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The frequency of advanced arteriosclerotic, renal and retinal lesions in youthful diabetics is becoming more fully appreciated. The total number of youthful diabetics in the United States is not accurately known, but the facts concerned with an estimate of the diabetic population available in 1946 were reviewed by Joslin *et al.*[11] Patients between the ages of 15 and 30 years include: (a) those whose diabetes began in childhood and have survived many years of diabetes, (b) those with diabetes beginning between 15 and 30 years, recognized and unrecognized, (c) finally, those who will sooner or later develop diabetes. The National Health Survey by the National Institute of Health in 1935-1936 disclosed 9,182 diabetics in an urban population of 2,500,000.[14] This information was based upon a house to house campaign but without tests of the blood sugar. However, surveys have become available based on actual blood and urine chemical tests which give quite a different picture. Thus, Blotner and Hyde[2] studied 45,000 consecutive selectees from ages 18 to 45 years at the Armed Forces Induction Station. They found diabetes to be about 3 to 4 times that of the National Health Survey. These figures were confirmed in a study by the National Youth Administration.[6] Among 147,813 youths age 16 to 24 years, glycosuria was present in 2.6%. There were 178 known diabetics, or 1.2 per 1,000. More recent still is the survey conducted by members of the United States Public Health Service in Oxford, Massachusetts, in which it was shown that for every 40 known diabetics there were 30 unknown cases. The estimated incidence for diabetes in this youthful period was 3 or 4 times that of the National Health Survey. In Table 1 are given the population at ages 15 to 45 estimated as of July 1, 1945, for the United States, and the frequency of diabetes in the youthful groups from an editorial in the Journal of the American Medical Association.[4]

TABLE 1.—DIABETES IN YOUTH

Population Continental United States July 1, 1945		Massachusetts Selectees		National Health Survey	
		Age	No. Diabetics per 1000 Registrants	Age	No. Diabetics per 1000
Age	**Total**	**All**	**4.6**		
All	139,621,431			**15-24**	**0.6**
15-19	11,651,506	18-25	**2.0**		
20-24	12,157,729	26-30	**3.5**		
25-29	11,469,639	31-35	**6.2**	25-34	**0.9**
30-34	11,006,658	36-40	**6.1**		
35-39	10,151,305	41-45	**10.6**	35-44	**2.0**
40-44	9,400,648				

An estimate of 36,523 cases of dia-

* Aided by grants from the Eaton Laboratories Fund and the Life Insurance Medical Research Fund.

betes between 15 and 35 years, based upon the National Health Survey, seems too low. Yet an estimate of 84,000 for the ages 15 to 30 years, based on Massachusetts selectees, may be excessive. One may safely estimate that there are at present between the ages of 15 and 30 years 60,000 cases of diabetes. More important, however, are the indications of a continued increase in the next few years. Thus the United States population may reach a maximum by 1985 when it will be 22% greater than it was in 1940.* At the same time the diabetic population may increase by 74%. One may safely add, therefore, to the total number of patients between the ages of 15 and 30 years who now have diabetes a minimum of 25%, or 15,000 who will develop it within the next few years.

The importance of vascular lesions in older diabetics has long been familiar to students of the disease. Now the excessive development of vascular nephritis, hypertension and retinitis in poorly controlled diabetics of long duration looms large on the horizon even in youth. Among 148 diabetics with onset of diabetes between 15 and 30 years of age, 64% show retinal hemorrhages and increased capillary fragility after 10 years of diabetes.[10] Although many influences, metabolic, infectious and endocrine may play important parts in the causation of these lesions at an early period, deficiency of one hormone, insulin, must be given primary consideration as the underlying factor. In youthful diabetics, the onset and course of vascular complications may be long observed. Additional necropsy data are needed, but are difficult to obtain owing to the improvement in treatment with consequent prolongation of life.

Between 1938 and 1946 clinical and post mortem records of the New England Deaconess Hospital include 10 patients whose diabetes began before the age of 20 years and 2 others with onset at 22 and 27 years with diabetes of 0.2 to 20 years duration. Millard and Root[9] found that in 5 whose diabetes was of less than 5 years duration, no vascular complications were present. In 7 of these 12 patients, whose death occurred at ages between 25 and 32 years, coronary arteriosclerosis with partial or complete occlusion was present. Nephrosclerosis was present in 6 of the 7 and intercapillary glomerulosclerosis was present in 3. The globular masses of hyaline material between or within the glomerular capillary walls described by Kimmelstiehl and Wilson, present in 3 cases, emphasize the fact that this lesion is as typical of diabetes in youth as in later life. A striking feature of the post mortem examinations of these 7 youthful cases with diabetes of more than 10 years duration is the fact that the arterial lesions are not of a single character. They involve all 3 of the common types: (1) calcification and sclerosis of the media of the Mönckeberg type; (2) intimal atheromatosis involving the aorta as well as the coronary arteries; and (3) arteriolar sclerosis evident especially in the kidneys, but also in splenic and pancreatic vessels. The lesions are identical with those seen in diabetes of later life. It must be concluded that it is the long duration of diabetes which in some way causes the lesions.

In the study of the pathology found at autopsy among 606 cases of diabetes, 290 males and 316 females, reported from the University of Minnesota by E. T. Bell,[1] 78% of the deaths were of persons over 50 years of age. Only 18 cases were under 20 years and 21 cases between 20 and 30 years of age. It does not appear from the discussion

* These estimates are based upon the "medium" forecast of population published by Thompson and Whelpton in Estimates of the Future Population of the United States, 1940-2000, National Resources Planning Board, Washington, D. C., Table 7, page 68.

that any material was available on patients whose diabetes began in childhood and who had survived 12 or more years of diabetes. Twenty % of the cases died in diabetic coma. Gangrene and coronary disease together accounted for 27.2%. Pyelonephritis accounted for 1% (6 cases), and uremia for 0.7% (4 cases). By combining deaths from coma, infection and vascular disease, Bell concluded that 66.3% of diabetics die of complications related to the diabetes. It is not strange that in a series lacking youthful patients with diabetes of long duration it would be easy to conclude that intimal thickening in small renal arteries occurred after the age of 50 years easily. After 50 years of age it was five times as frequent in the diabetics and was more intense than in the control series of non-diabetic autopsies. Yet Bell's 15 cases, aged 10 to 20 years, showed in 20% slight arteriolosclerosis and in 25% of 20 cases between 20 and 30 years of age arteriolosclerosis of grades 1 and 2 was present. It is this renal arteriolosclerosis which is a striking feature in the autopsies of our juvenile diabetic patients who have survived diabetes 12 to 15 years. Dr. Bell states that a thick homogeneous hyaline deposit in the arterioles is strong evidence of diabetes. It seems clear that in some way diabetes brings about at an early stage in life hyaline changes in the arteries and arterioles with consequent hypertension and renal disease. Possibly the hyaline masses in the glomeruli are so closely related to arteriolosclerosis that they should be regarded as dependent upon the same fundamental etiology. Certainly the large nodular lesions are almost pathognomic of diabetes. In Bell's series of 40 diabetics from 1 to 30 years of age, neither nodular nor diffuse "intercapillary" lesions occurred, but they were frequent from 50 years onward. The association of the "intercapillary glomerulosclerosis" with arteriolosclerosis and arteriosclerosis of larger vessels is evident in Bell's series and in our patients.

In the series of Gauld, Stalker and Lyall,[7] 12 of the 24 diabetics reported developed progressive renal complications after diabetes of long duration. In 6 of the 7 cases observed post mortem, Kimmelstiehl-Wilson lesions and nephrosclerosis were present. They also comment upon the presence of pyelonephritis in 3 cases.

That one must consider in diabetes not only the arteries but also the veins and capillaries has been clearly shown in recent years. Thus Root and Rodriguez[10] have studied capillary fragility in diabetes. In 26 cases with retinitis and increased capillary fragility, 11 were from 21 to 39 years of age. It is quite evident in young diabetic patients that change in capillary fragility occurs within 5 to 12 years after the onset of diabetes and is frequently associated with beginning evidences of vascular disease. Usually such patients will within a few months or a year or two begin to show retinal hemorrhages, subsequent to vascular disease. The nature of the change occurring in capillary vessels is yet undetermined and the place of such substances as rutin and ascorbic acid in its treatment is being investigated. In recent years increasing attention has been given to small venules in the retina. Dilatation of these venules and some of the hemorrhagic manifestations in the eyes in retinitis proliferans seems clearly due to disturbance in the veins.

These facts may indicate different etiologic factors are at work and that diabetes of long duration exerts a specific influence permitting early vascular damage of varying types. Clinical examination of 192 diabetics,[13] in whom diabetes began before the age of 15 years and who have survived 20

or more years of diabetes, showed calcified vessels by Roentgen-ray examination, albuminuria, hypertension or retinal hemorrhages in 86%. However, in 14% of these patients no such lesions were found, which gives hope that better treatment may postpone these changes in the future.

Three basic questions may be stated upon which divergent views have been expressed: (1) Is arteriosclerosis a cause or an effect of diabetes? There are still some physicians of experience who believe that arteriosclerosis causes diabetes. Such cases must be rare. Onset of diabetes declines in frequency from the age of 60 onward. No case in 2,500 childhood diabetics has shown hypertension or arteriosclerosis at onset of the diabetes or developed it until diabetes has existed for periods from 5 to 15 years. (2) Is arteriosclerosis a complication of diabetes or is it an integral manifestation of the basic disorder which causes diabetes? Dry and Hines[3] postulated an inherent weakness in the diabetic constitution which affects both the insulin-producing tissues and the vascular system with a common mechanism for the

TABLE 2.—CAUSE OF DEATH ACCORDING TO DURATION OF DIABETES
531 DIABETICS WITH ONSET PRIOR TO 30 YEARS OF AGE

Duration Diabetes at Death Years	Number Deaths	Coma %	Nephritis %	Heart %	Tuberculosis %	Pneumonia Sepsis %	Misc. %
0- 4.9	166	56	4	5	8	12	13
5-14.9	223	28	13	8	12	15	22
15-20 plus	142	3	30	32	7	9	19
Total Deaths	531	150	82	67	59	67	106

TABLE 3.—COMA AS CAUSE OF DEATHS IN YOUTH RELATED TO AGE AT ONSET AND DURATION OF DIABETES

Duration Diabetes at Death Years	Age at Onset 0-14 Years Deaths	0-14 Years Coma %	15-20 Years Deaths	15-20 Years Coma %	21-30 Years Plus Deaths	21-30 Years Plus Coma %
0- 4.9	78	71	37	46	51	38
5-14.9	95	31	37	16	91	18
15-20 plus	48	4	18	5	76	1

TABLE 4.—NEPHRITIS AS CAUSE OF DEATH RELATED TO AGE AT ONSET AND DURATION OF DIABETES

Duration Diabetes at Death Years	Age at Onset 0-14 Years Deaths	0-14 Years Nephritis %	15-20 Years Deaths	15-20 Years Nephritis %	21-30 Years Deaths	21-30 Years Nephritis %
0- 4.9	78	4	37	5	51	2
5-14.9	95	11	37	11	91	17
15-20 plus	48	48	18	22	76	23
Total	221		92		218	

TABLE 5.—CALCIFIED ARTERIES IN 82 YOUNG DIABETICS RELATED TO DURATION OF DIABETES

Duration Diabetes Years	Average Age	Number Cases	Arteries Calcified %	Calcification Present Aorta %	Pelvic Arteries %	Leg Arteries %
0-10	28.2	8	0	0	0	0
10-15	25.8	17	33.3	5.8	11.7	29.4
15-20	27.6	33	54.5	24.2	33.3	45.4
20-28	33.5	24	83.3	25.0	45.8	70.8

production of arteriosclerosis, retinopathy and neuropathy on the basis of involvement of the nutrient vessels to these structures. I disagree with this view. First, it would necessitate arteriosclerotic disaster for all diabetics, which in fact does not happen. Second, in time one should certainly find in some of the 2,500 children and another 2,000 with onset diabetes from 15 to 30 years of age, cases in which vascular disease preceded the diabetes. This has not been observed. (3 Are the arteriosclerotic complications of diabetes the result of changes characteristic of clinical diabetes? I believe the excessive arteriosclerosis in young diabetics of long duration is the result of uncontrolled diabetes and consequent features such as the poor resistance to infection with resultant pyelonephritis, pyorrhea, etc. In support of this view are cited 16 cases recently studied who now after 20 to 25 years of diabetes show no evidences of nephritis, arteriosclerosis by Roentgen-ray examination, or retinal hemorrhages.

Causes of Death in Diabetes with Early Onset. In Table 2 are shown the causes of death for 531 patients whose diabetes had its onset between infancy and 30 years of age. The series comprises 221 patients with onset of diabetes before their fifteenth birthday, 92 patients with onset between 15 and 20 years, and 218 patients with onset between 21 and 30 years. Coma caused 56% of 166 deaths occurring during the first 5 years of diabetes but thereafter it declined as a cause of death. In the group of 142 deaths occurring after 15 years of diabetes, it caused only 3%. The striking feature of this table is the increase in deaths from nephritis and arteriosclerotic heart disease to 30 and 32% of all deaths occurring after 15 years of diabetes. In Table 3 the place of coma in childhood is more clearly shown, since 71% of deaths occurring within 5 years after onset before the age of 15 years were due to coma. Its virtual disappearance as a cause of death after diabetes had been present 15 years applied not only to the childhood but also to the cases with onset of diabetes between 15 and 30 years of age. An analysis of nephritis as a cause of death is given in Table 4. It is evident that among deaths occurring within 5 years duration of diabetes nephritis plays little part, from 2 to 5%, or actually only 6 deaths among 166 total deaths. After 15 years of diabetes, 48% of 48 deaths in patients whose diabetes began in childhood and 22% of 94 deaths in the other groups present the crux of the problem in the treatment of youthful diabetics, for it is the association of the renal lesions with hypertension, retinitis and later coronary disease, which most concerns us.

The relation of duration of diabetes to onset and development of vascular and renal lesions may be studied in various ways. In Table 5 are summarized the results of Roentgen-ray examinations of pelvic arteries, leg arteries and of the aorta (lateral films) in young diabetics. No calcification was found in cases with average age 28.2 years and with diabetes less than 10 years in duration. Thereafter, as the duration of diabetes increased, the incidence of visible calcification rapidly increased until 83.3% of cases with diabetes of over 20 years' duration showed calcified arteries. The arteries of the leg usually, but not always, show calcification first. Granted that calcification is a late stage in arteriosclerosis, it is still significant and especially in the pelvic arteries, where its grave prognostic import in pregnant diabetics of long duration has been emphasized by Priscilla White.

The high incidence of renal and vascular disease has been thought to be due to infections, endocrine factors, disturbed mineral metabolism, and uncon-

trolled diabetes. While it is true that diabetic patients are susceptible to streptococcus and staphylococcus infections, this group has not shown prior to the incidence of vascular disease or nephritis infections which could be related to them, except for pyelonephritis. Sharkey and Root[12] pointed out the excessive frequency of pyelonephritis in diabetics of long duration. Determinations of basal metabolisms, analyses of blood for such pituitary factors as follicle stimulating hormone and the excretion of 17 ketosteroids in a limited number of patients have not shown a clear picture. However, the studies of Selye[11] demonstrate experimentally the production of nephrosclerosis by means of injections of pituitary extract and the use of high protein-high salt diets. When the relation between the control of the diabetes as measured by hyperglycemia, glycosuria, acidosis and the faithful adherence to a prescribed diet are tabulated, there appears a striking correlation between lack of diabetic control and the development of vascular lesions. Thus, in 28 cases among the 192 diabetic children who survived 20 years of diabetes, Roentgen-ray examinations and clinical studies were normal, and in this group coma had only occurred in 17%. In 114 cases, calcified arteries in the legs or pelvic vessels were present with transient albuminuria, with hypertension and only one or two retinal hemorrhages. In this group, coma had been present one or more times in 38%.

Fifty patients were incapacitated with angina pectoris, progressive nephritis, cerebral accident, retinitis proliferans, and in them coma had been present in 74% one or more times. Coma represents maximal lack of diabetic control.

In considering the eye lesions of this group, one must abandon the idea that the retinitis follows, or is consequent upon arteriosclerosis. The small round retinal hemorrhages, typical of diabetes, occur in patients without hypertension and before arteriosclerosis or albuminuria can be found. Frequently it is true these patients show increased capillary fragility and at present it appears probable these lesions are an essential and early stage of vascular disease. The striking thing about the retinal lesions of this young diabetic group is the tendency for progression from the stage of small hemorrhages to the stage of proliferation so commonly known as retinitis proliferans. In non-diabetics, on the other hand, small hemorrhages are frequently absorbed and only rarely stimulate proliferation of capillaries and fibrous tissue. This phenomenon is characteristic of a diabetic and seems in some way connected with the faulty metabolism of uncontrolled diabetes.

One must remember that, in the diabetic, disturbances of protein and fat metabolism, as well as of carbohydrate, do occur. To the ophthalmologist a faulty protein metabolism seems most likely to explain various phases of retinitis. The normal eye fluids contain no proteins only electrolytes, sugar and urea. Blood colloids are held back by the endothelium which is impermeable to colloids. There is an effective fluid exchange by osmosis. The abnormal ocular fluids contain protein and thereby break down the normal osmotic interchange. As a result the pressure within the eye increases. A breakdown of proteins in stagnant fluid gives toxic products promoting hemorrhage and the ingrowth of new capillaries. The abnormal kidney allows leakage of protein and edema.

Of 23 known amino acids, 10 are thought to be essential to life. The body can synthesize proteins from these amino acids in the liver. The body can form glycine but cannot form cystine, tyrosine or histidine.

Cystine is in a key position for the formation of amino acids into protein and it is a curious fact that in some diabetic patients there are hints of a disturbance in cystine metabolism. It is true that in diabetic animals made diabetic by alloxan a fall in the cystine of the blood occurs. Furthermore, administration of cystine impairs the effectiveness of alloxan in producing necrosis of the islands of Langerhans. This field is now being investigated with some promising preliminary results. One may say, therefore, that with respect to carbohydrate, fat and protein metabolism abnormalities occur in the uncontrolled diabetic, some of which may be directly related to the eye. Thus, the nitrogen balance in diabetic patients may be negative during periods of poor control and was often found negative during the early periods of treatment by under-nutrition. The evidences of liver disease affecting the formation of protein substances in diabetic patients is suggestive, although the large liver filled sometimes with glycogen, sometimes with fat, has not always been shown to be deficient in its protein-forming function.

The localization of the first evidences of arteriosclerosis is difficult. At present we try to carry out Roentgen-ray examinations af all diabetic patients in the juvenile group and of all other diabetic patients seen between the ages of 20 and 40 years. A summary of recent roentgenograms in 82 such cases is given in Table 5. We found that only 4 out of 24 patients with diabetes over 20 years failed to show visible calification either in the arteries of the legs, pelvis or the aorta. In patients with diabetes from 10 to 20 years, calification was absent in only 21 out of 50 patients. In 8 patients with diabetes less than 10 years, no calcification could be found. The average age when calcification was first seen varied from 26 years for the females with diabetes less than 20 years to 31 years for the females with diabetes over 20 years. Apparently the duration of diabetes is the most important factor. As just stated, no calcification was found in patients with diabetes of less than 10 years' duration; in the 50 patients having diabetes from 10 to 20 years the average duration of diabetes was 15 years when the first evidence of calcification was seen; in the patients with diabetes for more than 20 years the average duration of diabetes was 20 years when calcification was noted. The last 2 groups show little difference in average insulin requirement. Thus, 44 units was the average dose for patients of long duration and 50 units was the average dose for the 50 cases of shorter duration. The average blood cholesterol value at the maximal was 306 for the females of less than 20 years' duration and 285 for the females of more than 20 years' duration. Males averaged 242 mg. and 296 mg. In this group of 74 patients, therefore, an increased plasma cholesterol has been an almost constant finding, not necessarily at the onset of the diabetes, but at some time during the course of the diabetes and frequently during the stage when albuminuria, hypertension, hypoproteinia had developed. In a series of 26 young diabetics reported by Mann, Gardner and Root,[8] the plasma cholesterol values remained normal during the first years of diabetes, but became abnormally elevated on the average of 12 years after onset, when the first clinical evidence of renal disease became evident. In 36 patients the serum protein was over 6%, whereas in 18 cases the serum protein was under 6%.

Summary. The cause of death in patients whose diabetes begins in childhood and prior to the thirtieth year of age changes rapidly if death occurs after prolonged periods of the disease. Thus, acidosis and coma account for a majority of deaths which occur in the

first few years of diabetes, but it is only the cause of 3% of deaths in diabetic patients of this youthful group who survive more than 15 years of the disease. On the other hand, death from arteriosclerotic disease increased rapidly among those patients who have lived more than 15 years with diabetes. In patients with onset before 15 years of age, arteriosclerotic nephritis is a cause of 48% of the deaths which occur after 15 years of diabetes. In those patients whose diabetes begins between the fifteenth and thirtieth years, nephritis is similarly a major cause of death; but after 15 years of diabetes coronary disease becomes of equal prominence in this older group. The vascular disease of these young people is characterized by the fact that it affects all types of arteries. Atheromatosis of the larger vessels, arteriolosclerosis and medial calcification are found in various degrees The renal lesions also are usually mixed, including the typical lesions of Kimmelstiehl disease and also typical lesions of pyelonephritis and chronic glomerulonephritis. Endocrine factors, infections, but chiefly loss of control of the diabetes itself are the prominent etiologic factors. In diabetic children the greater the frequency of diabetic coma, the more advanced the degree of vascular lesions found after a period of 15 years. Nevertheless, arteriosclerosis is not inevitable. Many cases after 20 years of diabetes fail to show retinal lesions or vascular disease. When the extraordinary improvement in the treatment of diabetes which has followed the introduction of insulin is considered, one cannot help but be optimistic for the future and refuse to "sell American medicine short."

Conclusions. Vascular disease in diabetic patients in youth involves not merely the arteries and arterioles but also the veins and capillaries. Increased capillary fragility and retinal hemorrhages often are early findings. Changes in the retinal veins are common. Renal complications associated with vascular disease include the Kimmelstiehl-Wilson syndrome, hypertension, edema and albuminuria with hyalinization of arterioles. Chronic pyelonephritis is frequently the cause of renal failure, occasionally in association with arteriolosclerosis and nephrosclerosis, and occasionally glomerulonephritis. The striking fact that all types of arterial disease occur in these young diabetic patients after years of diabetes may suggest multiple etiologic factors—infections, endocrine and metabolic. However, the development early in life, the definite relationship between degree of diabetic control and the severity of these vascular lesions speak for an intracellular vulnerability to various etiologic factors conditioned by diabetes itself.

An estimate of 75,000 patients who now have diabetes or will soon develop it between the ages of 15 and 30 years in the United States is conservative. The need for a concerted study of the relations between the character of diabetic control, the proper use of insulin, the management of infections and the development of vascular disease in the kidneys, retina and heart stands as a challenge to pathologists and internists alike.

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STUDIES IN HEPATIC GLYCOGEN STORAGE: I. ADRENALIN-INDUCED HYPERGLYCEMIA AS AN INDEX OF LIVER FUNCTION * †

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The production of hyperglycemia and glycosuria following the injection of adrenalin, was demonstrated by Metzgar,[13] Paton,[14] and Blum[4] shortly after the turn of the present century. It was subsequently demonstrated that such adrenalin-induced hyperglycemia failed to occur following hepatectomy in experimental animals and following ligation of the hepatic artery.[8,12,15,17] Loeper and Verpy[11] first evaluated blood sugar response in humans with liver damage, as contrasted to normal controls, and thought that the procedure could properly be utilized as a test of liver function. Brill in 1929,[5] Sucksdorff in 1930,[16] Althausen and his coworkers,[1,2,6] Loeb, Reeves, and Glasier in 1931,[10] and Cantarow and Ricchiuti in 1934[7] re-evaluated the procedure as a clinical test of liver function; but concluded that the adrenalin response was too unpredictable to permit its use as a quantitative instrument.

In all of the investigations above mentioned, adrenalin was administered in dosage varying from 0.3 to 1.0 cc. of 1:1000 solution by hypodermic injection, to individuals whose dietary intake had been subject to no standardization in the days preceding the test. Bierry and Rathery[3] showed that adrenalin hyperglycemia may be significantly modified by diet. It seems probable that the inconstant results obtained by previous workers are referable to lack of adequate preliminary standardization (see later).

We first became interested in the procedure from a non-hepatic aspect; that is, from the standpoint of variation of hepatic glycogen storage in certain endocrinopathies. The investigation was pursued initially in a somewhat sporadic fashion, being chiefly concerned with the obtaining of control data in medical students and house officers, with an occasional observation on patients with endocrinopathies and hepatopathies. This portion of the work was

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finished in 1944, and will be noted below as **Phase 1.**

Phase 2 began in the Philippines in 1945. One of us, L.K., observed hundreds of patients suffering and convalescing from acute epidemic hepatitis. The majority of these patients on a regime of rest and adequate diet became clinically well within 4 weeks of the onset of jaundice. Those of us responsible for the management of these men had 3 major problems:

1. To determine, as early in the disease as possible, which men would convalesce in average time with a simple rest-diet regime, and which would develop the more serious degrees of hepatitis, requiring more strenuous therapy and prolonged hospitalization.

2. The evaluation of the effectiveness of therapeutic measures such as plasma, blood, and protein hydrolysate infusions.

3. The matter of determining when a post-hepatitis patient was ready to return to duty.

Considerable data were obtained during this period. Because of the lack of optimal control in some phases of the study, a report was delayed until such time as the work could be repeated on a smaller group under adequately controlled conditions.

Phase 3, begun in 1946, constitutes such a controlled study. The observations made in the tropics, under poorly controlled conditions, have been confirmed (see below).

Results. *Phase 1:* Only data on normal controls obtained during this period will be considered at this time. Liver glycogen storage in endocrinopathies and in response to hormone administration will be reported in a separate publication. Fifty-four observations were obtained on 39 adult males during this period. A dose of 0.01 cc. of 1:1000 solution of adrenalin (10 micrograms) per kg. of body weight was arbitrarily selected as the standard amount to be administered intramuscularly. This dose has been used throughout this study except in a few individuals, in whom 4 sets of values were obtained–2 with the dose noted above, and 2 with larger dosage. No significantly greater blood sugar response was obtained in any instance with the larger dose.

By way of preparation, all control subjects received a high carbohydrate intake for 3 days prior to the test. The importance of this in other "carbohydrate" tests has previously been stressed.[9] Initially, the procedure was: 1. Fasting blood specimen for sugar determination; 2. Administration intramuscularly of 0.01 cc. 1:1000 adrenalin per kg. body weight; 3. Blood specimens at 15, 30, 45, 60, 90, 120, 180 minutes for sugar determination.

The curves so obtained, with rare exceptions, were essentially identical with those obtained in a normal glucose tolerance test. A composite presentation of the above data is shown in Figure 1.

In all but 1 instance in the first 20 controls, the maximal rise was obtained between the 30 and 60 minute periods. Since the purpose of the test was to measure maximal adrenalin response (maximal hepatic glycogenolysis), the procedure was simplified by obtaining only 0, 30, 45, and 60 minute blood samples and reporting the test in terms of difference between the fasting and maximal post-adrenalin blood sugars. This shorter procedure was followed in all subsequent tests.

These data show that blood sugar elevation in response to adrenalin administration under standard conditions in normal individuals ranges from 40 to 100 + mg. per 100 cc., with an average value of 58. This maximal elevation is obtained within 60 minutes following adrenalin administration.

Phase 2. 143 tests of hepatic glycogen

storage were performed on military personnel, all suffering or convalescing from acute epidemic hepatitis. Of these, 110 performed on 76 patients were reasonably well controlled from the standpoint of a diet adequate in calories and high in carbohydrate (by mouth or intravenously) for one or more days prior to the tests. The remainder could not be controlled adequately and are not included in these data. Long standing malnutrition in some of those patients included in the controlled group may very possibly have affected the adrenalin response, irrespective of the actual hepatic status of the individual. This was the major factor which led us to await Phase 3 before reporting our findings.

For descriptive purposes, the patients have been divided into 3 groups on the basis of intensity of the jaundice, and duration of the disease. Group 1 includes individuals with a maximal icterus index of 30 units and a duration of clinical jaundice of not more than 2 weeks. Group 2, those with a maximal icterus of 60 and maximal duration of jaundice of 4 weeks. Group 3 includes all those with the most severe form of the disease. The findings are shown in Fig. 2. In more than 80% the glycogen storage test values included in these averages were obtained during the first 2 weeks of clinical jaundice. The correlation of the adrenalin response with the clinical course of the disease, and with the icterus index seems obvious.

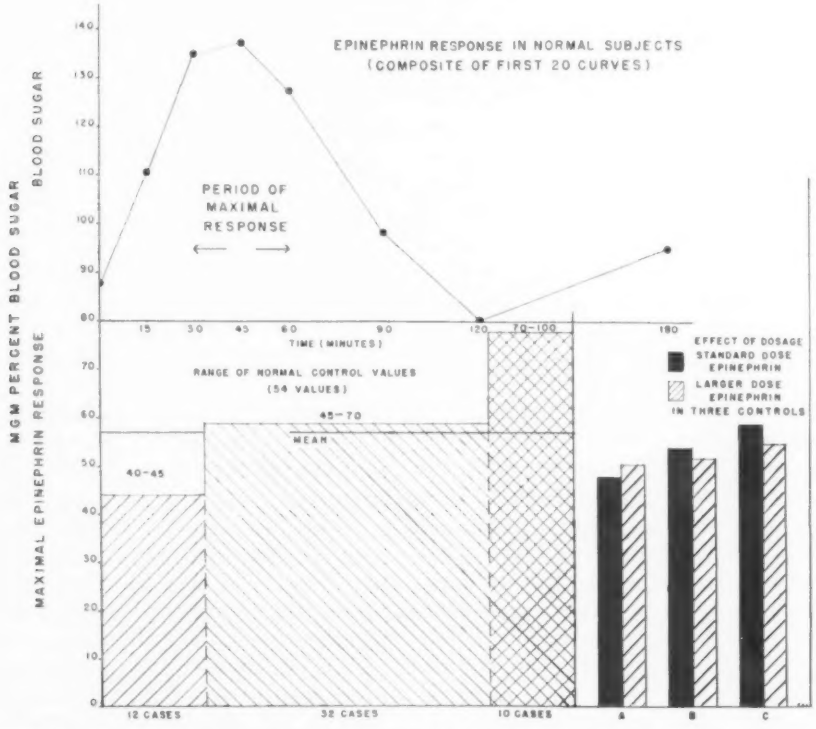

FIGURE 1.—Hepatic glycogen storage test—Adrenalin response in normal subjects, showing average curve, range, mean, and effect of dosage. The larger dosage does not significantly increase the maximal response.

Correlation with other liver function tests, and serial values in the same individual will be considered under Phase 3.

As stated before, 3 major questions needed to be answered in these men:—(a) *Early Determination of the Probable Severity of the Disease.* It will be noted that the average response to adrenalin in the first and second weeks of the disease in Group 1 was within the normal range, and that glycogen storage test values in Group 2 more closely approached the normal than did those in Group 3. (b) *Evaluation of the Effectiveness of Therapeutic Agents.* Aside from diet, the only therapeutic agents used in this phase of the program were plasma, and protein hydrolysates. To our considerable surprise, hydrolysates seemed to cause a more prompt clinical and chemical improvement than did plasma. This will be discussed further in another report. (c) *Determination of Complete "Cure" of the Hepatitis.* The glycogen storage test was not found to be a reliable index of "cure" in the sense of complete readiness for full activity. The adrenalin response usually became normal in the presence of an abnormal cephalin flocculation.

Phase 3. With the inauguration of the present University of California-Navy research program in the pathologic physiology of the liver, the further evaluation of this test under precisely controlled conditions was given high priority.

Technic. The 3 day high carbohydrate, iso-caloric or hyper-caloric intake previously noted has been continued. In addition, between 8 and 10 p.m. the night preceding the test, the individuals under study received 8 ounces of fruit juice fortified with 2 ounces of glucose, the obvious purpose of all these measures being to obtain maximal storage of glycogen in the liver.

Clinical Material. Over a period of almost 2 years, a large group of patients with acute hepatitis in all phases and of all degrees of severity has been studied. The same statement applies to men with cirrhosis, *i.e.*, chronic, advanced liver damage, usually alcoholic in origin.

A small group of patients with chronic, non-resolving, viral hepatitis has also been the subject of intensive study.

All these men have been under unusually well controlled conditions with regard to food intake, activity, and clinical and chemical evaluation. A number have been on balance study regimes; that is, have had absolute constancy of dietary intake during most of their period of study.

CLASSIFICATION	NUMBER OF PATIENTS	MAXIMAL DURATION OF JAUNDICE	MAXIMAL ICTERUS INDEX	MAXIMAL EPINEPHRIN RESPONSE
MILD HEPATITIS	20	2 WEEKS	30	46
MODERATE HEPATITIS	34	4 WEEKS	60	32
SEVERE HEPATITIS	22	LONGER	200+	19

FIGURE 2—Adrenalin response of patients studied in Phase 2, with mild, moderate, and severe hepatitis. There was little overlapping between the 3 groups.

Findings. *Acute Hepatitis.* In Fig. 3 are shown serial studies of 10 patients selected essentially at random from several score of such individuals. All 10 men were less than 30 years of age and had "classical" forms of the disease; all were severely jaundiced when first studied; all but one had histological confirmation of the diagnosis by one or more biopsies; and all eventually made complete chemical and clinical recoveries. Total bilirubin values are not shown in some instances because of the use instead, of the icterus index.

PATIENT BAB—Clinically this man made a moderately slow, but otherwise uneventful

recovery, and returned to his work as a butcher approximately 5 months after the clinical onset of the disease. He was readmitted to the hospital 3½ months later with a recurrence (or reinfection), from which he has apparently completely recovered. The meaning of the variability of his glycogen storage test response during convalescence from the recurrence is not apparent to us at this time.

PATIENT BRO—had an initially intense, but

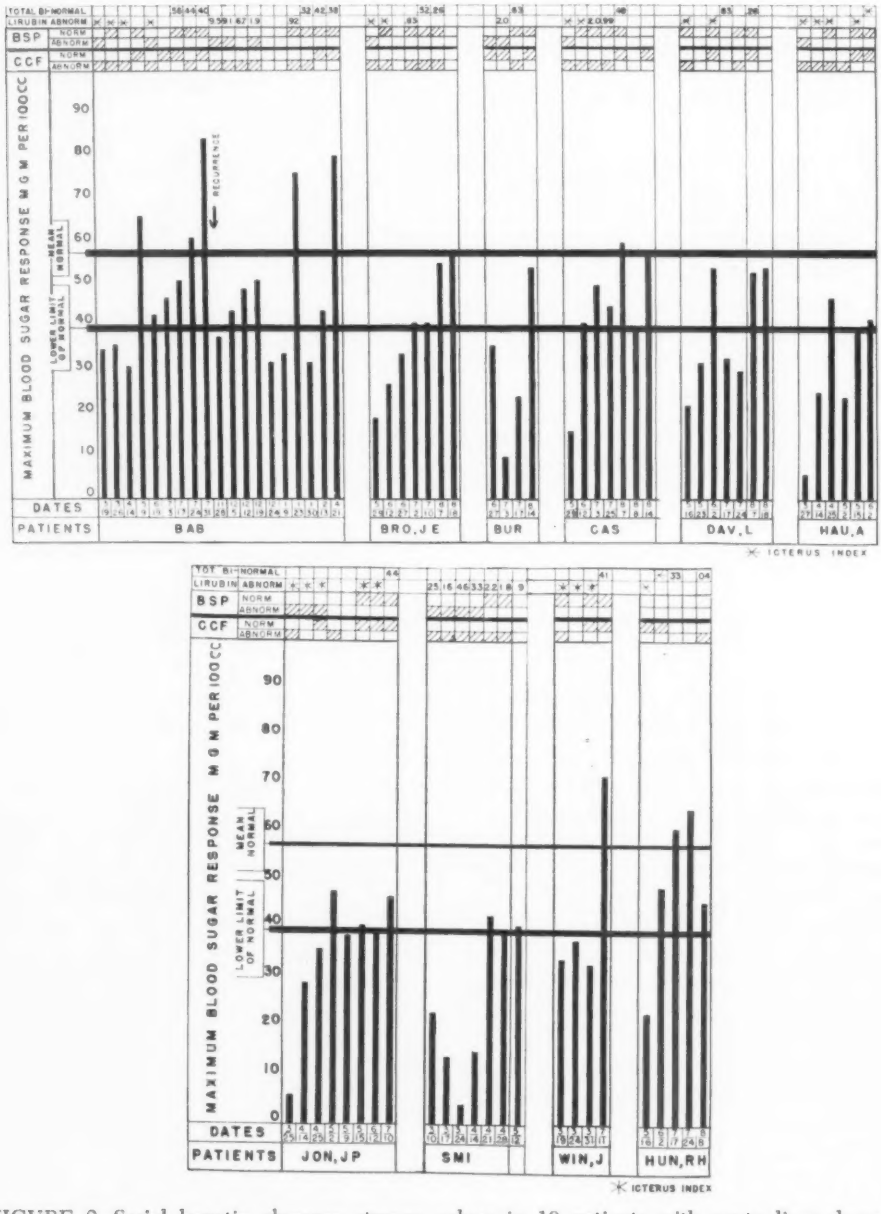

FIGURE 3—Serial hepatic glycogen storage values in 10 patients with acute liver damage (hepatitis), including correlation with 3 standard tests of liver function.

rapidly resolving hepatitis, the course of which is well indicated by the glycogen storage test.

PATIENT BUR—shows a glycogen storage test pattern which has been observed in many of these men—a normal or nearly normal value in the first day or two of the disease, followed by a drop to very low levels, and then a gradual rise, sometimes to high normal levels, the latter indicating, perhaps, major hepatocellular regeneration.

PATIENTS CAS, DAV, HAU, JON, SMI, WIN, and HUN—show varying degrees of the above findings.

As in the case of all tests of liver function with which we are familiar, there is no really close correlation of the glycogen storage test with any other laboratory procedure. In Fig. 4

LIVER FUNCTION TEST	CORRELATION	NO CORRELATION	NUMBER OF OBSERVATIONS
CEPHALIN CHOLESTEROL FLOCCULATION	63%	37%	140
BROMSULFALEIN RETENTION	61%	39%	132
THYMOL TURBIDITY	60%	40%	78
ICTERUS INDEX	66%	34%	101

FIGURE 4—Correlation of glycogen storage test with 4 other liver function tests in a random group of patients with acute and chronic liver damage.

are findings in patients with acute and chronic liver damage, selected at random, indicating a correlation of this determination with 4 other simple tests of liver function considerably more than would be obtained by chance, and showing a surprising closeness of per cent correlation in all 4 tests.

Chronic Liver Damage (Cirrhosis). In Figure 5 are shown serial studies in 10 patients with cirrhosis of varying extent and acuteness. The findings in these men are capable of more exact interpretation than are those in the patients with hepatitis, because of the more slowly changing nature of the disease in the majority of instances. As in the hepatitis patients, the diagnosis has been proven in each individual by one or more biopsies.

PATIENT BEA—This 35 year old man was admitted in a hyperacute phase of a long standing cirrhosis. The acute flare-up was induced by a combination of an alcoholic debauch and congestive heart failure. His liver was loaded with fat. On adequate dietary and cardiac management, he made a rapid response, which is reflected in his glycogen storage test as well as in the other tests of liver function.

PATIENT DAN—This man had a typical, severe, alcoholic cirrhosis of approximately 20 years duration. During the entire period covered by the data presented (excepting only the last 2 values), he was under well controlled conditions on the hospital ward. During this time he made slow but steady clinical improvement. The last 2 values were obtained several months after the patient had left the hospital and was on a program of essentially full activity. The final glycogen storage test value was obtained after an all night bus ride without adequate preparation in terms of preliminary high carbohydrate intake. Inasmuch as he was clinically vastly improved at this time, it can be assumed that this final value emphasizes the need for adequate preliminary preparation for the test.

PATIENT DRE—was one of the few patients in our group with irreversible, progressive liver damage. He died a few weeks after the last test shown.

PATIENT GRA—Very similar to patient BEA—an acute, severe flare-up of a long standing cirrhotic process. He eventually was discharged free of symptoms, although with considerable permanent damage to the liver.

PATIENT HAN—An aged male with pronounced intrahepatic portal hypertension and, to date, intractable ascites. We cannot explain the one normal bromsulfalein value.

PATIENT HAW—A young, alcoholic male, with a large liver showing surprisingly little fibrosis. Perhaps his extremely high glycogen storage test response may be explained on the basis of a liver in a hyperregenerative phase. Similar findings have been observed in one other comparable patient.

PATIENT NIB—A middle aged alcoholic

male with histologic evidence of major liver damage, but free of ascites. The very abnormal glycogen storage tests in the presence of a normal bromsulfalein test emphasizes the value of this procedure as part of a panel of tests of liver function.

PATIENT PAR—A middle aged alcoholic cirrhotic, originally admitted with extreme ascites which disappeared with adequate dietary management. The peaks in the values of his tests are referable to specific therapeutic procedures—this is discussed elsewhere.

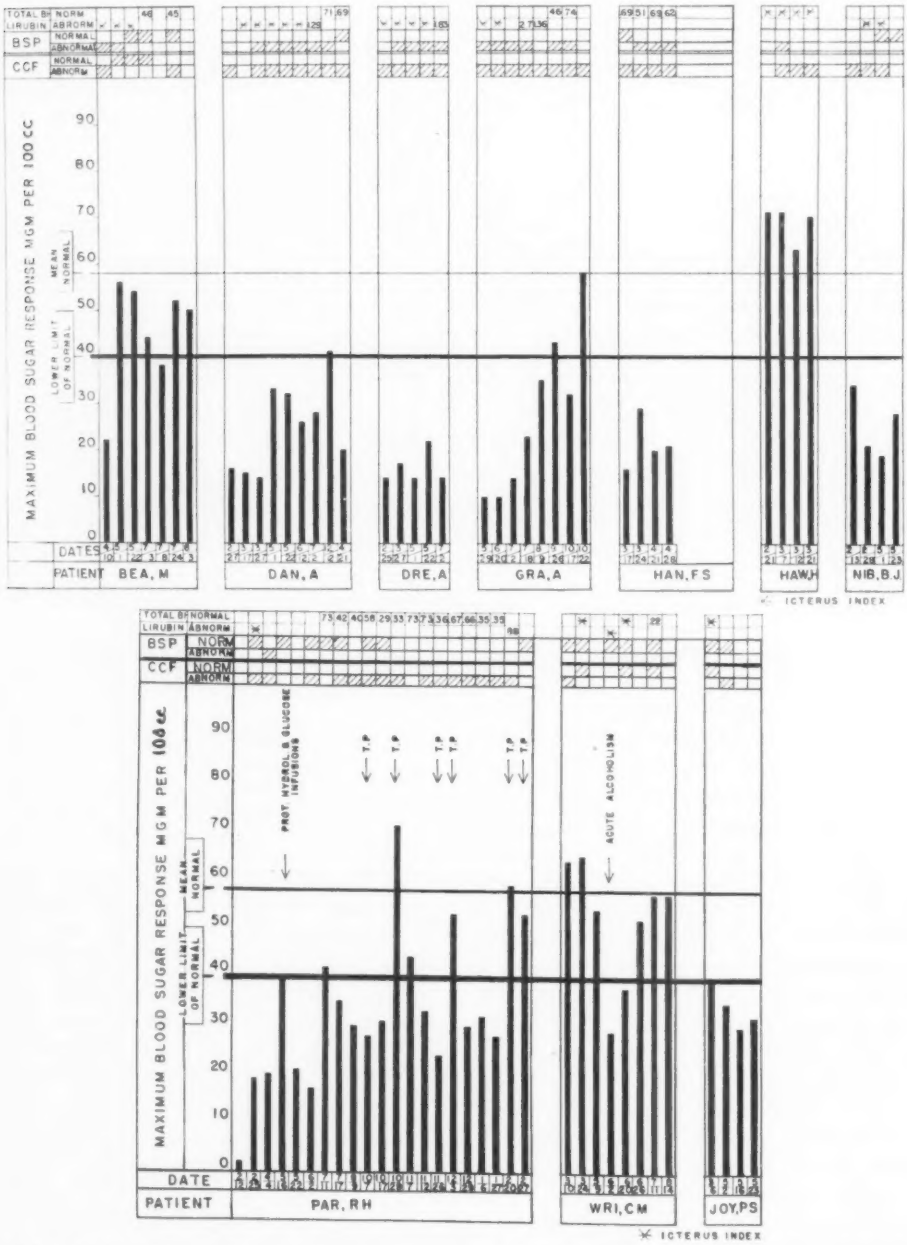

FIGURE 5—Hepatic glycogen storage in 10 patients with chronic liver damage (cirrhosis)

In him, as in NIB, the observation of abnormal glycogen storage test values in the presence of normal bromsulfalein findings is striking.

PATIENT WRI—A young alcoholic cirrhotic with surprisingly normal chemical findings despite highly abnormal clinical and histological findings. It is interesting that the abnormal glycogen storage test and a barely abnormal icterus index were the only chemical reflections of a major alcoholic debauch.

PATIENT JOY—A middle aged male in the same category as NIB.

Chronic (viral) Hepatitis. The data on these men are included in another article devoted to a discussion of this pathological entity. Suffice it to say here that for the most part the glycogen storage test findings correlate well with other laboratory observations.

Discussion. The data here reported are representative of more than 2,000 individual observations obtained over a period of 5 years. It is our very strong conviction that one contributes nothing to clinical or laboratory medicine by adding new, inconclusive procedures to an already badly confused field. It is our hope and belief, for the following reasons, that the glycogen storage test does not fall in this category:

1. Any panel of tests of liver function should include some procedure which provides a clue to the carbohydrate metabolic activity of the liver. The glycogen storage test, as contrasted to procedures based upon the oral or intravenous administration of sugars, supplies essentially unequivocal information, in that the initial elevation of blood sugar, in response to adrenalin, can relate only to pre-existing hepatic glycogen. It is theoretically possible that muscle glycogen, broken down to lactate in response to adrenalin, and then re-synthesized to hepatic glycogen might affect the shape of the curve if one followed it over a 2 to 3 hour period. This is of only academic interest insofar as the present report is concerned.

2. From the representative data here reported, it is apparent that the glycogen storage test may supply evidence of hepatic abnormality which is not supplied by other function tests. It is equally obvious that the glycogen storage test does not in any sense replace such standard procedures as the bromsulfalein and the cephalin cholesterol flocculation tests. It is again emphasized that the reliability of the test is dependent upon a careful standardization of conditions during its performance.

Summary. The blood sugar response to a standard intramuscular dose of adrenalin in the normal adult, under standard conditions, is predictable and dependable. This response is appreciably diminished in patients with acute and chronic liver damage, but reverts to normal with its improvement. The procedure may therefore properly be used as one of a "panel" of tests of liver function.

Hemorrhage from esophageal varices has recently been observed in one man some hours post-adrenalin. It may be that the association of splenomegaly and esophageal varices should be regarded as a contraindication to the procedure.

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THE EFFECT OF BENZOIC ACID AND CARONAMIDE ON BLOOD PENICILLIN LEVELS AND ON RENAL FUNCTION*

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Since 1943, various substances which will interfere with the tubular excretion of penicillin have been studied. Diodrast[2,12,13] and para-amino hippuric acid[4,11] have proven to be effective but must be given by continuous intravenous administration in large doses and are not clinically practical for this reason. Benzoic acid[8,9,15] sodium benzoate, and more recently caronamide†[3,5,6] have been used orally. With the exception of caronamide all are thought to act by blocking the tubular excretion of penicillin. Bronfenbrenner and Favour[9] reported 4 to 7-fold enhancement of blood penicillin levels when benzoic acid was given orally but found that severe fluid and salt restriction was necessary to accomplish this. Spaulding, Bondi, and Early[15] also reported favorably on the use of this substance for enhancing blood levels of orally administered penicillin. Boger and Baker[7] have recently reported failure to increase blood penicillin levels by the use of benzoic acid when fluid and salt intake was not restricted.

In the last few months, several papers have appeared which deal with the clinical use of caronamide.[7,10] All have reported the effectiveness of this substance in increasing blood penicillin levels. Rather exhaustive renal studies in dogs have been carried out by Beyer,[5] who has been unable to find any evidence of renal damage from this drug. Boger and Baker[7] have reported that the administration of caronamide will increase the blood penicillin levels by about 8-fold and that this effect can be achieved at any dose level of penicillin.

To determine the clinical usefulness of such a drug two questions must be answered. (1) When administered orally over a long period in amounts that will be tolerated by the patient, does the drug effectively increase the blood penicillin level? (2) Under these circumstances, does the drug produce any renal damage? As far as caronamide is concerned, the question of renal damage seems to have been well answered in the negative. There is no available information of this sort concerning benzoic acid. This report is presented in an effort to answer the above questions.

Methods: The penicillin blood levels were determined by the reductase method of Reid and Brewer.[14] This method gave good reproducible results within the range of blood con-

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† "Staticin" Caronamide (4 Carboxyphenylmethanesulfonalide) was furnished through the courtesy of Sharpe and Dohme, Inc., Philadelphia, Pennsylvania.

centrations found in our subjects and has the advantage over other methods in that there is a sharp endpoint and one that is easy to read. The method was checked by repeated determination of known concentrations of penicillin in saline and in serum and was also checked against the Rammelkamp method. Under all these circumstances it was found to be adequate. All determinations were carefully controlled for the presence of the so-called "antisubtilis factor".[14] Determinations were usually made within a few hours of the time the blood sample was withdrawn and when this was not feasible the serum was promptly separated and frozen. Blood urea nitrogen levels were determined by the method of Archibald[1] and the endogenous creatinine clearances were determined by the usual Jaffe reaction using a tungstate filtrate.

Plan of Study and Results. *Benzoic Acid*—Nine patients in the Intensive Treatment Center (7 with early syphilis and 2 with central nervous system syphilis) were selected as subjects for this study. All were free from evidence of any other disease, particularly renal or hepatic, except 1 who showed consistently a diminished creatinine clearance without other evidence of disease. At the start it was thought that the patients could be studied while receiving the routine treatment of mapharsen, penicillin and bismuth but it soon was discovered that mapharsen caused a sharp, though temporary, reduction in renal function. Consequently the patients used in this experiment received only penicillin. No attempt was made to limit either fluid or food

TABLE 1.—BLOOD PENICILLIN LEVELS AND BLOOD UREA NITROGEN LEVELS IN PATIENTS RECEIVING 12 GM. OF BENZOIC ACID DAILY

Patient	Average Blood Penicillin Level Units/cc.		Average Blood Urea Nitrogen Mgs/100 cc.		Creatinine Clearance cc./min.	
	before Benzoic Acid	after Benzoic Acid	before Benzoic Acid	after Benzoic Acid	Initial	Final
D.R.	0.20	0.17	17	14	57	60
S.V.	0.20	0.10	11	18	82	87
Man.	0.07	0.20	11	18	92	99
Mar.	0.08	0.23	28	27	92	131
A.T.	0.11	0.10	18	9	70	69
An.	0.16	0.09	21	19	144	145
L.H.	0.22	0.28	23	31	115	124
J.V.	0.12	0.14	18	13	94	103
H.P.	0.04	0.09	17.5	14.7	129	82

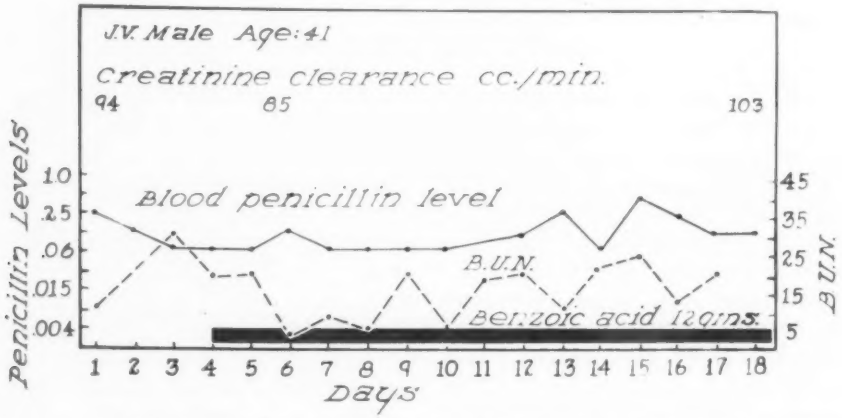

Chart 1.—The blood penicillin level, blood urea nitrogen, and creatinine clearance of 1 patient who received 12 gm. of benzoic acid per day for 14 days. None of these was significantly different from control levels.

intake during the experimental periods. Crystalline penicillin G in saline was administered intramuscularly to all subjects in doses of 30,000 units every 3 hours. The control period was started after the subjects had received penicillin for 18 to 24 hours. Penicillin and blood urea nitrogen levels were determined daily one and one-half hours after the most recent dose of penicillin and the endogenous creatinine clearance was measured at the beginning and end of the experimental period and in some cases on the fifth day as well. After a 4-day control period, 12 gm. of benzoic acid divided into 8 doses was administered orally for the next five days to all the subjects except one, who received this amount of benzoic acid for 14 days.

The results of these observations are summarized in Table 1. It may be seen that of the 9 subjects, there was some increase in the average blood penicillin levels in 3, no essential change in 3, and a lower average level in 3. Individual charts, however, show that the changes were not constant from day to day and that there was really little essential change over the control level. One Patient (J. V.) did show about a 2-fold enhancement but only after receiving benzoic acid for 7 days (Chart 1). The blood urea nitrogen levels showed no consistent alteration beyond the rather wide variation from day to day that is to be expected when the patient is receiving the usual hospital diet. In no case did the endogenous creatinine clearance show any significant change from the control period. Routine urinalysis also failed to show any abnormality.

Caronamide. Twelve patients (5 luetics and 7 convalescent from various infectious diseases) were used as subjects. All were free from evidence of renal or hepatic disease. Blood penicillin levels were determined daily at 1 and 3 hours after an injection of penicillin. All subjects received aqueous penicillin intramuscularly at 3 hour intervals, but did not necessarily receive the same dose. Each individual subject, however, did receive the same amount of penicillin throughout the experiment. After a 2 day control period, the patients were given caronamide in doses varying from 12 to 24 gm. per day in 8 equal doses for the next 3 days. In addition to these short term studies, combined penicillin and caronamide therapy was maintained for at least 1 month in 2 subjects. Each patient received 24 gm. or more of caronamide per day. Penicillin levels

TABLE 2.—BLOOD PENICILLIN LEVELS IN PATIENTS RECEIVING CARONAMIDE DAILY

Patient	Control Period Penicillin/cc. blood		Dose Caronamide	While receiving Caronamide for					
				24 hrs.		48 hrs.		72 hrs.	
	Av. 1 hr.	Av. 3 hrs.	Grams/24 hrs.	Penicillin/cc. blood at					
				1 hr.	3 hrs.	1 hr.	3 hrs.	1 hr.	3 hrs.
Gi.	0.5	0.12	24	4.0	1.0	16.0	1.0	16.0	2.0
O.	0.5	0	24	0.5	0.12	2.0	1.0	2.0	1.0
Ge.	0.25	0.09	24	0.5	0.06	1.0	0.5	2.0	0.25
Du.	0.18	0	24	1.0	0.25	0.12	0.06	0.5	0.06
J.B.	0.31	0	20	4.0	0.5	1.0	0.12	2.0	1.0
C.P.	0.5	0	20	1.0	0.12	0.25	0	0.25	0.06
Hic.	0.5	0.09	16	0.5	0.12	0.5	0.5	2.0	0.5
D.D.	0.25	0.06	16	0.5	0.06	0.5	0.12	1.0	0.25
Ke.	0.25	0	12	1.0	0.06	1.0	0.12		
St.	0.09	0	12	0.12	0.06	1.0	0.12	0.5	0
Sm.	0.12	0	12	0.06	0	0.12	0	0.5	0
Carl.	0.12	0	12	0.06	0	0.12	0	0.25	0

were determined 2 or 3 times a week. The purpose of this part of the experiment was not so much to determine enhancement of the blood penicillin levels as to evaluate the feasibility of administering caronamide over a long period.

The results of the caronamide study are shown in Table 2. It may be seen that doses of 12 and 16 gm. per day failed, in most cases, to alter the blood penicillin level significantly. Doses of 20 to 24 gm. per day, however, gave this patient it became necessary at times to increase the penicillin dosage. Therefore, the actual increase in blood penicillin levels cannot be ascribed wholly to caronamide. We were particularly interested in one phenomenon, shown in Chart 3. After administration of 24 gm. of caronamide per day for 8 days, the penicillin levels fell off rather sharply and symptoms recurred. When the dose of caronamide was increased to 32 gm. per day the blood penicillin levels became stable and

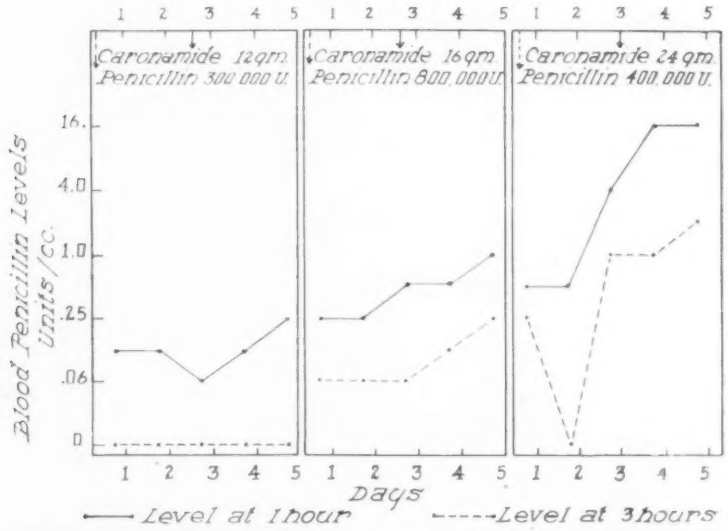

Chart 2.—The effect of various doses of caronamide on the blood penicillin level of individual subjects. The arrows indicate the time at which the administration of penicillin and caronamide, respectively was begun.

4 to 16-fold increases in the blood penicillin level (Chart 2). It is of interest to note that in a number of cases the blood penicillin levels were higher 48 and 72 hours after beginning caronamide than at 24 hours. It is noteworthy too that in many cases caronamide produced a greater relative increase in the blood penicillin level at 3 hours than at 1 hour after injection.

The results in 1 of the 2 patients with subacute bacterial endocarditis are shown in Chart 3. In the treatment of remained so during the rest of the time that caronamide was being administered.

This patient, who died on his 96th hospital day, received a total of 1650 gm. of caronamide in 58 days. At autopsy the kidneys were grossly normal and on section showed no abnormality that could be attributed to the drug. This suggests that this drug even in large doses for long periods does not damage the kidneys.

Discussion. From the above data, it is evident that the administration of 12 gm. of benzoic per day has little effect in enhancing the blood penicillin levels. It is true that this quantity is not as great as others have used, but preliminary observations convinced us that this dosage was about all that the usual patient would tolerate over a long period of time. Even with this relatively small amount, about one third of the patients complained of gastric burning and some anorexia. It is entirely possible that had salts and fluids been strictly limited, the levels might have been higher but such restriction over several days is difficult at any time and in the presence of a febrile illness would be undesirable. Boger and Baker[7] used up to 24 gm. of benzoic acid per day and demonstrated no increase of the blood penicillin levels. We were unable to demonstrate any evidence of renal impairment during the administration of benzoic acid over periods up to 14 days and conclude that this drug, in the doses used at least, does not damage the kidney.

Caronamide, on the other hand, when given in doses of 20 gm. a day or more appears to be an effective agent for increasing the blood penicillin levels, and has the additional advantage that no limitation of salt or fluid seems to be necessary. More important, perhaps, is the ability of caronamide to prevent the rapid decline of blood penicillin levels between injections during intermittent parenteral administration.

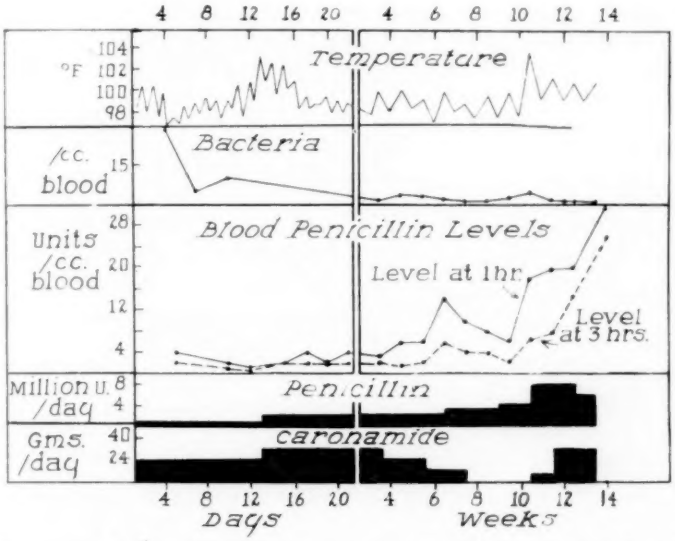

Chart 3.—Summary of data obtained in 1 patient with subacute bacterial endocarditis. In that portion of the chart designated by weeks, the amount of caronamide and penicillin administered is indicated as the average per day for that week.

Note the sharp pre-mortal rise in the blood penicillin level.

We have found this drug to be ordinarily well tolerated by the patients. About one-quarter of the patients complained of mild anorexia which seemed to correlate best with the number of pills they were taking. No severe reactions attributable to caronamide were observed.

We did not determine the blood or

urine caronamide levels of any of the subjects in this series. Such measurements may prove to be useful for adjusting caronamide dosage. We believe, however, that the alteration of the blood penicillin level gives a good index as to the effectiveness of the caronamide dosage and at the same time offers more useful clinical information than the caronamide level. This is well illustrated in Chart 3.

It has been stated by a number of investigators that in the treatment of most of the infectious diseases that respond to penicillin, higher levels are easily obtained by simply increasing the dose of penicillin and that the various enhancing agents are of no great clinical value. In general, we are in accord with this view. However, in certain diseases, particularly subacute bacterial endocarditis and those infections caused by an organism with a relatively high resistance to penicillin, caronamide is a valuable adjuvant to therapy, and combined penicillin and caronamide will result in higher and better sustained levels than can be obtained by the use of any reasonable dose of penicillin alone.

Summary and Conclusions. 1. In the presence of normal fluid and electrolyte intake, benzoic acid was ineffective in enhancing the blood penicillin level. In doses of 12 gm. per day for periods of 14 days or less no measurable renal damage was observed.

2. Caronamide in suitable dosage is an effective agent for increasing and prolonging the blood penicillin concentration.

3. One patient received 1650 gm. of caronamide and showed no damage to the kidneys when these were examined post mortem.

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PROGRESS
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RADIOLOGY

UNDER THE CHARGE OF

HARRY M. WEBER, M.D.
AND
DAVID G. PUGH, M.D.

SECTION ON ROENTGENOLOGY, MAYO CLINIC
ROCHESTER, MINNESOTA

THE NORMAL ROENTGENOGRAM OF THE CHEST IN INFANTS AND CHILDREN

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THE determination of normal in roentgenograms of the chest in infants and children is difficult because of the constantly changing appearance of the chest owing to the growth and development of the child. By definition, normal means "according to or constituting an established norm, rule or principle." In deciding what is to be the standard of normal in an infant or child, proper latitude must be provided to include those normal variations in morphology which are secondary to the normal growth and development of the child and which are without significance in the diagnosis of disease.

In addition to the effect of growth and development on the roentgenogram of the chest there are also obvious mechanical problems associated with obtaining roentgenograms of the chest in infants and children. In the adult in most cases it is possible to obtain the patient's co-operation, so that roentgenograms of the chest are fairly uniform with respect to the phase of respiration and the position of the chest on the roentgenogram. With children, on the other hand, even with care in roentgenography it is difficult to obtain uniform results. Roentgenograms may be made in almost any phase of respiration; position is difficult to control and rotation of the patient may produce apparent changes in the roentgenogram, making interpretation difficult. Even with restraining devices motion is difficult to control. Clothing and hair braids, muscle and soft tissue shadows seem to be more confusing in the interpretation of roentgenograms of the chest in infants and children than in adults.

Interpretation of the roentgenograms of the chest in infants and children depends on a consideration of these factors that will influence the appearance of the roentgenogram but the diagnosis of normal is not directly related to these factors, except that they may act to obscure and confuse the correct diagnosis. The roentgenographic diagnosis of normal depends on the recognition of a progression of changes which take

place in the healthy child, which are evident on the roentgenogram of the chest and which are not associated with disease.

In order to determine what should be included in the range of normal in infants and children and also to determine, if possible, the time, nature and degree of any changes in the roentgenographic appearance of the chest that might be associated with their growth and development, I reviewed the thoracic roentgenograms of several hundred children. These children had no symptoms referable to the chest or evidence suggesting pulmonary disease. All these roentgenograms had previously been reported as negative.

In reviewing these roentgenograms I tried to correlate the roentgenographic findings with the age of the infant or child. For the purposes of interpretation, the structures of the chest represented on the roentgenogram were divided into: 1, the bones of the thoracic cage and shoulder girdle; 2, the aorta, pulmonary vessels and mediastinal shadow, exclusive of the thymus; 3, the cardiac silhouette; 4, the bronchovascular markings; 5, the diaphragm; 6, the lungs; and 7, the thymus. The age groups of these infants and children were also arbitrarily divided into: 1, newborn through the first month; 2, 1 month through 12 months; 3, 1 year through 3 years; 4, 4 through 7 years; 5, 8 through 12 years. These various age groups were not determined until after the roentgenograms of the chest had been reviewed and then the separation into these various age groups seemed to be a rather natural procedure in view of the findings as noted on the roentgenograms.

Birth Through the First Month. In most of the roentgenograms of the chest in newborn infants the ribs are perpendicular to the spinal column and encircle the thorax at the same level that they leave the spinal column. This varies somewhat with the phase of respiration and occasionally the more adult type appearance is seen with anterior downward slope of the ribs. The body of the scapula and the acromion process, as well as the clavicles, are fairly well formed, although the coracoid process is not well developed. The epiphysis of the head of the humerus can be seen as a small, rounded area of increased density between the upper end of the shaft of the humerus and the glenoid fossa of the scapula.

The shadow of the aorta is not seen. The pulmonary vessels are also very difficult to identify. The mediastinal shadow, which seems to be proportionately wide, is produced by the thymus and the cardiac silhouette.

Cardiac size and shape are extremely variable in newborn infants. Farrell[2] has classified the heart shape into 4 groups: 1, long narrow; 2, broad apical with a narrow base; 3, broad apical with a broad base; and 4, round globular. The second and third types make up the great majority of cardiac contour types in infants. Determination of cardiac size in infants is not wholly satisfactory, possibly because the phase of respiration affects the cardiac contour proportionately more in newborn infants than later in life. Weymuller, Bell and Krahulik[9] stated that accurate measurement of the cardiac shadow on the roentgenogram is technically impossible because of the great individual variation in cardiac size and contour. Farrell[2] measured the heart size in newborn infants and found that the cardiothoracic index was 0.55, only 0.05 greater than that taken to be normal in adults. Most investigators are agreed that although there is probably some cardiac enlargement the first and second days of life, there is probably a fairly regular tendency toward reduction in the size of the heart as mani-

fested on the roentgenogram after the second day.

In my experience the bronchovascular markings were proportionately smaller and less distinct in the newborn infant than in older persons.

The diaphragm assumes varied contours peculiar to the individual. It may be domeshaped, flat or even conical. Caffey[1] stated that the conically shaped diaphragm tends to be present more frequently early in life than later but the shape of the diaphragm, once established, does not change appreciably during growth to adulthood. Proportionately the extent of diaphragmatic motion is about the same in infants and children.

The lungs of stillborn infants are seen as a homogeneous dense shadow on the roentgenogram of the chest. In the living infant at birth, air enters the atelectatic lung, causing expansion of the alveolar spaces. In some cases the process of expansion is incomplete and atelectatic areas are noted in the roentgenogram of the chest. Wasson[8] has pointed out that on the one hand these may be small patches of increased density in the lung involving only small regions of parenchyma or on the other hand whole lobes may be unexpanded. The time required for complete expansion of the lungs has been estimated by Wasson[8] to vary from 5 minutes to 2 weeks. Solis-Cohen and Bruck[6] reported an incidence of 4% of cases of newborn infants with atelectasis. Weymuller, Bell and Krahulik[9] reported 1 infant in 25 who presented roentgenographic evidence of incomplete expansion of the lungs. The bases of the lungs are probably the last portions of the lungs to become completely aerated. Atelectasis due to incomplete expansion of pulmonary tissue is probably not often seen after the first few days of life. Wasson[8], and Weymuller, Bell and Krahulik[9] described linear markings in the lungs of newborn infants that are fairly prominent and can be traced well out to the periphery of the lungs. These markings are seen rather frequently, but disappear after the first few weeks of life. The reason for their presence is not entirely clear. They may be associated with incomplete expansion of the lung but their continuity with hilar shadows suggests that they may be related to some adjustment in the pulmonary circulation which takes place early in life.

Farrell[2] reported the presence of a roentgenographically recognizable thymus in measurable chests in a little less than one third of his cases of newborn infants. It is probable that roentgenograms made in the expiratory phase would demonstrate a much higher percentage of thymuses. The incidence of a thymus in newborn infants depends on what is interpreted as thymic shadow. In my experience there is a recognizable thymic shadow in practically all newborn infants, although there is great variation in its size and shape. Classifications devised to describe the numerous thymic outlines become too complicated because of the protean character of the organ.

One Month Through 12 Months. From 1 month through 12 months the thoracic cage does not change appreciably. The ribs in most cases are similar in position to those of the newborn infant. The capital epiphysis of the humerus grows in size and presents an oval appearance.

The aorta is not visible because on leaving the heart it passes directly upward, backward and down. The pulmonary vessels may be seen. If measured they are found to proportionately larger with respect to the size of the chest than later in life.

The cardiac size gradually decreases during the first year of life, and when the child is 1 year old the ratio of cardiac size to chest size is approxi-

mately that of the adult. Cardiac size is probably in normal ratio after 6 months.

The peribronchial and perivascular markings become better defined during the first year, but they are less noticeable at this time than they are during the next year of life. The lungs in the region of the cardiophrenic angles are still relatively clear, and the peribronchial and perivascular markings that can be seen are more or less confined to the immediate region of the hilus of the lung.

The diaphragm in this age group is not remarkable. The diaphragmatic level varies between the eighth and the tenth ribs posteriorly, depending on the degree of inspiration and on individual constitutional structure of the child and the characteristic appearance of the diaphragm.

The growth in length of the child gives the lungs a more adult appearance. There are generally no areas of fibrosis or calcification encountered in the lungs in infants of this age.

The thymus is usually still present if it was seen roentgenologically at birth. Wasson[7] has stated that the thymus continues to enlarge up to 1 year of age, after which it begins to decrease in size. My experience has been that most of the thymuses that are seen at birth are smaller by the time the infant is 1 year old. Perhaps this is due to a difference in the rate of growth of the infant's chest and the thymus, with the chest growing faster than the thymus.

One Year Through 3 Years. In the average infant, the ribs begin to shape downward anteriorly between 1 and 2 years of age, and usually by the time the child is 2 years old the ribs have reached the relative position and shape they will maintain throughout life. The clavicles and scapulae are well formed. The epiphysis for the greater tuberosity of the humerus appears near the age of 2 years, and the proximal end of the humeral shaft acquires a pointed or conical shape. The aortic shadow is still not seen. The mediastinal shadow, composed of the bases of the great vessels and the thymus, is narrower, partly owing to growth in length of the chest and partly to regression of the thymus. The pulmonary vessels are still slightly larger in proportion to the entire chest but between the second and third years this disproportion disappears.

The cardiac silhouette has assumed its normal relative proportion to the rest of the chest, and although the shape varies with the individual there is nothing remarkable about it.

During the period between 1 and 3 years of age the child usually learns to walk and spends relatively more of his time on his feet. Beginning at 1½ years of age there was noted an increase in the bronchovascular markings in the roentgenogram of the chest. The appearance of the bronchovascular markings on the roentgenogram may be influenced by: 1, the amount of overlying soft tissue; 2, the phase of respiration; 3, the exposure factors used in obtaining the roentgenogram; and 4, the amount of connective tissue present in the peribronchial and perivascular tissues. If all these factors are taken into consideration there is still a relative increase in the prominence of the bronchovascular markings between 1½ and 3 years. It has been suggested that there may be some disproportion in growth between the bronchi and vessels and the parenchyma of the lung. Wasson[7] has stated that there is a relative increase in the bronchovascular markings from birth to 3 years of age. In my experience there is a gradual increase in these markings between 1½ years and 3 years. In the 3 year and 4 year age groups they are most marked, being proportionately more evident than in

the adult, except for the aged. Maresh and Washburn[3] pointed out that in follow-up studies of infants and children the variation in the prominence of bronchovascular markings is as much a part of individual changes in growth and development as differences in size and shape of the cardiac silhouette. In the opinion of these authors, each child establishes his own normal for the appearance of the hilar shadows and pulmonary markings soon after birth, and these characteristics are maintained throughout life without any consistent relation to the amount of infection that may be present in the accessory sinuses of the head.

The diaphragm in this age group was not remarkable. The average diaphragmatic level with respect to the ribs was between the ninth and tenth posterior ribs. In the roentgenograms reviewed for this age group the diaphragm appeared to be flatter and less dome-shaped. There was no apparent explanation for this fact.

The pulmonary parenchyma is not remarkable in this age group, and in the average child no pulmonary parenchymal shadows are seen on the roentgenogram.

In my experience the shadow of the thymus is usually smaller at 1 year of age than at birth, and it decreases in size until by 3 years of age it has disappeared. Very little of the shadow of the thymus remains to be seen at 2 years of age. Wasson stated that the shadow of the thymus in children usually disappears by the twenty-sixth or twenty-eighth month. Mosher, Macmillan and Motley[4] reported that roentgenograms of the chest in 2,344 children from 1 to 16 years of age demonstrated thymic shadows in 7.5%. Of these, 20% were seen at 1 year of age, 23% at 2 years, 20% at 3 years and 10% at 4 years, with the remainder more than 4 years of age.

Four Through 7 Years. The bones of the thoracic cage and the shoulder girdle do not show any appreciable change early in this age group. The epiphyses of the head of the humerus and the greater tuberosity of the humerus begin to fuse. The ribs, clavicles and scapulae show the evidences of growth that may be expected. The cortex is somewhat thicker and the trabeculation of medullary bone is more well defined.

In the average child the aortic knob is not seen. The pulmonary vessels are proportional to the size of the chest.

The cardiac silhouette is of normal shape and size.

The bronchovascular markings in the 3 year to 4 year age group, which seem to be more prominent and proportionately heavier than in older children and adults, gradually become less marked and assume a normal adult proportion as the child reaches the 5th to the 7th year.

The appearance of the diaphragm is not significant in this group.

The pulmonary parenchyma occasionally shows a small area of fibrosis or a tiny area of calcification in normal children in this group between 4 and 7 years. It may be argued that a roentgenogram of the chest that demonstrates fibrosis or calcification in a child is not normal. On the other hand, such findings in an otherwise healthy, normal child without any previous history of recognized disease are rather difficult to explain, unless they can be classified within the limits of normal.

The thymic shadow in the normal child has disappeared by this time.

Eight Through 12 Years. Probably very few roentgenologists would agree now with a statement made over 25 years ago that "the chest of a child (from 6 to 10 years of age) from a roentgenologic standpoint is subject to such wide variation within normal limits as to be beyond the possibility of

exact description[5]." With present-day equipment it is possible to obtain roentgenograms of a quality that makes exact description easier. By the time the child has reached 8 years of age, the relative proportions of the bones of the thoracic cage, the heart, lungs and other structures have reached a ratio which is relatively normal in proportion to the chest as a whole. The aortic knob can frequently be identified. Areas of calcification and fibrosis in the lung are not uncommon and calcification in the hilar nodes is also fairly frequent.

Conclusions. The roentgenograms of the chests of infants and children present somewhat different findings from those of adults, and the range of normal is wider in infants and children than in adults. The variants of normal in infants and children are associated with the growth and development of the child.

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THERAPEUTICS

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FOLIC ACID AND ANTAGONISTS IN NEOPLASTIC DISEASE

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ATTEMPTS to affect the course of neoplastic disease in animals and man by the internal use of chemical agents have met with limited, though measurable success. Chemotherapeutic agents of demonstrable activity include arsenicals, benzol, urethane, and nitrogen mustards. These may be regarded as effective by virtue of a selective injury to proliferating cells (see reviews by Karnofsky[42], Gellhorn and Jones[28]). The mechanism underlying selective damage may be related to actions against basic metabolic functions common to all cells. Nevertheless, specific susceptibility of proliferating cells to such derangements could result from their greater dependence on synthetic mechanisms to supply the needs of growth and cell division. Alternatively, the complex mechanisms underlying cell division may involve unique biochemical processes exhibiting specific susceptibilities to the actions of chemical agents. Accordingly, non-dividing cells are less affected. Similar considerations based on the relatively rapid rate of growth characteristic of many malignant tissues have stimulated investigations into the possible relationship between deficiencies of vitamins and the course of neoplastic diseases[10]. The requirements of rapidly growing malignant tissues for accessory growth factors may be relatively great, thus rendering them susceptible to retardation or even inhibition by vitamin deficiencies induced in the host. Since vitamins are known to be key components of co-enzyme-prosthetic groups of enzymes[10,17], reductions of amounts available to malignant tissues may have the same chemotherapeutic result as the agents mentioned above.

Evidence specifically relating vitamins and malignant growth was considered unimpressive as recently as 1944 in a detailed review of the subject by Burk and Winzler[10]. Since that time, however, new investigations have demon-

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strated the potential chemotherapeutic value of deficiencies of certain vitamins of the B-complex. Of specific interest to the present review are studies suggesting the dependence of the growth of a variety of tumors on the utilization of folic acid. These studies followed the elucidation of the structure of folic acid and the subsequent synthesis of a series of closely related structural analogs which act as specific antagonists of folic acid. This review deals with the current knowledge of the latter substances, not as regards proven usefulness as chemotherapeutic drugs, but concerning the demonstration that anti-metabolites can inhibit growth of tumors.

Folic Acid as a Vitamin. In order to understand the function of folic acid in the development of neoplastic tissues, it is essential to consider the manifestations of folic acid deficiency in normal tissues. It is, therefore, of value to review briefly the current status of folic acid in nutrition of various organisms. Only some of the landmarks in the history of the vitamin will be mentioned. For more detailed information the reader is referred to excellent reviews of others[1,4,14,41,68,90].

The name "folic acid" was first applied to concentrates of spinach containing an active principle required for the growth of certain microorganisms[59]. The vitamin has been isolated in pure form from liver[65,78] and from yeast[5]. Proof of its structure was obtained by the synthesis of pteroylglutamic acid (PGA)[35,88]. Two conjugates of the vitamin containing varying numbers of glutamic acid residues have been isolated from natural sources, namely, pteroyltriglutamic acid[36] (see reviews by various authors[1] and by Jukes and Stokstad[41] for proof of structure) and peteroylheptaglutamic acid[66,67].

The requirements of many lactic acid bacteria as well as other species for PGA have been well established (see review by Jukes and Stokstad[41]). The growth of a ciliated protozoon has also been found dependent on PGA[43]. Among insects larval development of the mosquito *Aedes aegypti* is possible in the absence of folic acid but pupation does not occur[29]. The larval development and pupation of the flour moth, the flour beetle, and the meal worm, fail in the absence of adequate levels of PGA in the diets of these insects[23,30].

Studies on folic acid requirements of birds and mammals have revealed proliferating tissues to be selectively dependent for normal activity on the presence of adequate levels of the vitamin. Thus a cardinal feature of folic acid deficiency in warm-blooded organisms is a derangement and depletion of myelopoiesis and erythropoiesis. Inadequate levels of the vitamin in the diet of chicks lead to anemia, leukopenia, and thrombocytopenia, as well as poor feathering and inadequate growth[11,34,65]. Rats receiving purified diets, supplemented by sulfonamide drugs to suppress vitamin-synthesis by intestinal flora, develop anemia and granulocytopenia as the result of inhibition of myelopoiesis and erythropoiesis. Such lesions respond promptly to the administration of PGA[18,62,75,96]. In monkeys the feeding of diets low in PGA leads to granulocytopenia, megaloblastic erythropoiesis with attending macrocytic anemia, and various disorders of the digestive tract with lesions of the oral mucosa and diarrhea[16,47,91,92]. The satisfactory response of the deficiency-disease in monkeys to administration of PGA has its counterpart in various human macrocytic anemias which are amenable to therapy with the vitamin. Successes achieved in alleviating signs and symptoms of sprue, macrocytic anemias of infancy and pregnancy, and

megaloblastic anemias refractory to parenteral liver therapy, as well hematological remissions produced in pernicious anemia, have evidenced the nutritional importance of folic acid as a factor for normal hematopoiesis in man (see reviews[4,14,41,68,90]).

Conjugated forms of PGA, pteroyltriglutamic acid, pteroylheptaglutamic acid, and pteroyldiglutamic acid, appear to be as effective as PGA in alleviating folic acid deficiency in birds and mammals[5,15,36,79,96]. Presumably the activity of the conjugates results from enzymatic hydrolysis of the polyglutamyl portions with release of free PGA. Enzymes designated as "conjugases" have been found in a variety of tissues capable of releasing PGA from the more complex conjugates[6].

The administration of pteroyldiglutamic acid, pteroyltriglutamic acid, and pteroylheptaglutamic acid in normal humans is followed within a few hours by increased levels of free PGA in blood and urine[40,73,81]. The concentrations achieved approximate those following the administration of molar equivalent doses of unconjugated PGA.

Folic Acid Antagonists. After it had become evident that PGA is an essential metabolite for the maintenance of myeloid and erythroid tissues, it was logical to assess its role in neoplastic tissues, especially those of hematopoietic origin. While some success has been achieved in preventing the growth of at least one experimental tumor by dietary restriction of folic acid (see below), investigations in this field have been largely concerned with the chemotherapeutic potentialities of potent antagonists of PGA. The possibilities inherent in the use of analogs to antagonize the biological actions of vitamins were first established by Woods[94] in the classic demonstration of antagonism between sulfanilamide and para-aminobenzoic acid in microorganisms. A satisfactory generlization of the actions of metabolite antagonists has been made by Wooley[95]. ". . . a metabolite functions by first combining with a particular cellular unit which is usually regarded as an enzyme or possibly some other specific protein. . . . Now, in order for the first step to occur, the metabolite must possess certain structural features and the firmness of combination with the protein is determined in part by these. A similarly constituted compound is able to undergo this combination, but since its structure is not identical with that of the metabolite, its firmness of union will be different. The conjugate of analog and protein is, however, a new and foreign compound and is unable to proceed through the rest of the cycle of reactions. Like the fabled dog in the manger the analog denies the organism the use of the metabolite and thus creates a deficiency of the latter."

The first analog of PGA found to antagonize the vitamin in mammals was a crude product synthesized to contain a methyl-substituted pteroylglutamic acid, referred to as "X-Methyl folic acid"[24,25]. When the agent was added as a supplement to deficient diets in concentrations several thousandfold greater than that of PGA, characteristic signs of PGA-deficiency in mice, chicks, and rats were accelerated in appearance and enhanced in severity. The syndrome was readily prevented or successfully treated by administration of elevated levels of PGA. In later studies with mice[89] and pigs[12,32], species relatively resistant to deficient diets, supplements of X-methyl folic acid caused hematological lesions which readily responded to treatment with the vitamin. In pigs the signs of the deficiency resembled sprue in the appearance of megaloblastic anemia, leukopenia, and diarrhea.

Many additional analogs of PGA have been prepared exhibiting antagonisms toward the biological actions of folic acid in one or more microorganisms, birds, or mammals. Of present interest is a related series of antagonists which was introduced by the synthesis of 4-aminopteroylglutamic acid (4-amino-PGA[71]). The series is characterized by the replacement of the 4-hydroxyl of PGA with an amino group with varying modification of the remainder of the molecule. Observations of the effects of 4-amino-PGA in mice, rats, and chicks proved it toxic and even fatal within a few days after administration in diets in concentrations which were approximately equivalent to the amounts of PGA present[26,64,83]. Simultaneous administration of PGA provided only limited protection against the toxic actions of the congener.

The potency of 4-amino-PGA, its rapid effects, and the fact that its actions are not readily prevented by PGA, has raised the question whether it is a true folic acid antagonist. However, the sites of its primary actions are confined to the bone marrow and mucosa of the intestinal tract in guinea pigs[58], mice[85], rats, and dogs[69,86]. Changes in bone marrow are consistent with the effects of folic acid deficiency. Mice exhibit depletion of nucleated erythroid elements[85] and rats, guinea pigs, and dogs show a marked reduction of all hematopoietic elements. Moreover, in dogs, erythropoiesis becomes partly megaloblastic, a finding which has been observed with regularity in patients undergoing treatment with 4-amino-PGA and its congeners[3,87]. Damage to bone morrow and megaloblastic erythropoiesis and also destruction of the intestinal epithelium are marked within 24 hours after the administration of lethal doses of 4-amino-PGA. Similar changes are observed following the use of less potent analogs of 4-ameno-PGA, namely 4-amino-N_{10}-methyl-pteroylglutamic acid and 4-amino pteroylaspartic acid[22,70,26a].

On the basis of the evidence just summarized it has been concluded that the administration of 4-amino congeners of PGA in effective doses induces signs of PGA-deficiency[70]. The extreme nature of the lesions noted and the rapidity of their onset warrant the use of the term, "absolute deficiency," in descriptions of the syndrome reproduced by these agents. The agents may quickly deprive dependent cells of the vitamin resulting in metabolic derangement and, in turn, necrosis.

Effect of PGA and Conjugates on Experimental Tumors. Leuchtenberger *et al.* reported in 1945 complete regression of 38 of 89 spontaneous breast cancers in 3 different strains of mice treated with daily injections of 5 micrograms of an *L. casei* factor[49,52]. The percentage of spontaneous regression was only 1% as compared with 43% of their injected animals. The same group of workers reported inhibition of growth of transplanted Sarcoma 180 with folic acid concentrates and fermentation *L. casei* factor (pteroyl-triglutamic acid, teropterin, PTGA) in short term experiments[50,51].

These results could not be confirmed by subsequent investigations[72,80,97]; neither did PTGA nor PGA, when injected into mice inoculated with leukemic cells inhibit the development of the leukemia or prolong the life of experimental animals[77]. Moreover, treatment with 100 mg. per kg. per day of PGA failed to inhibit the growth of sarcoma T241 in mice[80a]. Doses of 50 mg. per kg. per day had no inhibitory effect on mammary adenocarcinoma (E0771), Harding-Passey melanoma, Wagner osteogenic sarcoma, and Patterson lymphosarcoma in mice, nor on sarcoma 39 and Flexner-Jobling carcinoma in rats[80a]. Furthermore, no

growth inhibiting effect of PTGA was noted on Sarcoma 180 or the spindle cell tumor Ma387 growing on the chorioallantoic membrane of the chick embryo[77].

Effect of PGA and Conjugates on Human Tumors. Farber and coworkers[19] studied the effect of pteroyldiglutamic acid (diopterin) and PTGA on 90 cases of advanced carcinoma and sarcoma in man. The tumors included gliomata of brain, sarcoma of bone, acute leukemia, lymphosarcoma, Hodgkin's disease, seminoma, and carcinoma of tongue, pharynx, esophagus, stomach, colon, rectum, kidney, bladder, prostate, cervix uteri, ovary, and gall bladder. No curative effect was noted after an average period of treatment of 5 weeks with average daily doses of 20 mg. of either drug. Only a few temporary regressions in size of subcutaneous nodules or of large metastases were seen. Many patients improved in morale and felt better from being given a new drug and much attention. In some cases, however, there was also a diminution in pain and in requirement for sedation or analgesis.

A later report[56] described the effect of PTGA on 7 cases with chronic lymphoid leukemia, 2 with chronic myeloid leukemia, 2 with multiple myeloma, and 2 with acute lymphoblastic leukemia. The patients were treated for periods of 4 to 10 weeks with doses ranging up to 200 mg. per day. In the cases of acute lymphoid leukemia PTGA appeared to convert the acute course into a chronic one. In the other cases there was no effect. Further studies[48] of 20 cases of advanced widespread cancers treated with PTGA for periods of 1 to 3 months with daily intramuscular injections of 50 mg. failed to reveal objective evidence of tumor regression. Nevertheless, dramatic clinical improvements were described. Laboratory studies showed a decrease of abnormally elevated alkaline or acid phosphatase but no changes in hematology. All patients exhibited a sense of well being and often the requirement for opiates was decreased.

Another group[84] treated 35 patients with advanced carcinoma. Twenty to 50 mg. of PTGA were given intramuscularly twice daily for periods of 2 weeks to 12 months. In 34 cases no change in the natural course of the disease was noted. In one case, however, a complete regression of metastatic nodules of a breast cancer in the lung followed 3 months of daily doses of 40 mg. A further case of regression in advanced metastatic breast carcinoma was reported in a patient receiving PTGA but previously treated with oophorectomy and testosterone[44,45].

Since some of the findings reported above created widespread interest and expectation, the Council on Pharmacy and Chemistry of the American Medical Association[2] deemed it necessary to explore the current status of PTGA and diopterin in the treatment of human cancer. On the basis of results submitted to the Council of 154 cases treated with PTGA and 121 cases treated with diopterin, it was concluded that the agents had no specific anti-carcinogenic effects. This conclusion is supported by experiences mentioned above with experimental tumors in which the majority of investigators failed to find tumor-inhibiting action by either PGA or its conjugates. Indeed it would be paradoxical to find folic acid in free or conjugated form acting as a growth-inhibitor.

Effect of PGA Deficiency and Antagonists on Experimental Tumors. As mentioned previously the role of folic acid for the maintenance of proliferating tissues stimulated studies of the influence of deficiences on

the growth of neoplastic tissues. Working with a single strain of New Hampshire red chickens susceptible to Newcastle disease, Little and coworkers[53,54] showed that the growth of Rous sarcoma could be controlled by regulating the amount of PGA in the diet of chicks. The authors reported the failure of Rous sarcoma to "take" or develop in one day old chicks maintained on PGA-deficient diets for 21 days after inoculation with the tumor; controls died with tumors within 16 days after inoculation. Small amounts of folic acid added to the diet stimulated tumor growth. However, in 6-week old birds kept on the folic acid deficient diet Rous sarcoma "took" in 60%. Subsequent therapeutic studies with 4-amino-PGA and related antagonists were carried out on baby chicks, 1 and 2 days old, maintained on a diet permitting tumor growth[53,55]. In the chicks tumor development was inhibited in a high percentage of cases. The compounds were found to be toxic and, while preventing the development of tumors, killed the chicks with signs of folic acid deficiency. In 4- to 9-week old chicks with established Rous sarcoma a tumor-inhibiting effect of 4-amino-PGA and 4-amino-pteroyl aspartic acid (4-amino-PAA) was also seen. In eggs, however, 4-amino-PGA, in doses fatal to the embryo within 4 to 7 days, failed to inhibit the growth of Rous sarcoma on the chorioallantoic membrane[42a].

The effect of 4-amino folic acids was studied on mouse tumors, Sarcoma 180 and Ma387, growing on the chorioallantoic membrane of embryonated eggs. The tumors were well established on the 12th day when the yolk sacs were injected with the compounds. Sarcoma 180 showed severe damage with cytoplasmic vacuolation and widespread necrosis. Sarcoma Ma387 showed only minor damage. Both tumors, however, were still viable on bioassay in susceptible mice. The doses necessary to produce lesions in the tumors were lethal to chick embryos[42a,77].

Extensive studies with 4-amino-PGA and related antagonists were carried out in mice (AKM) with different strains of leukemia[8,77]. The survival time of treated mice after inoculation with leukemic cells was compared with that of controls as a measure of tumor inhibition. The 4-amino compounds were given first 48 hours after the leukemic cells were injected. Treatment was continued 3 times weekly for 10 doses. It prolonged survival time in varying degrees for different strains but produced no cures. Furthermore, mice with an established leukemia injected with supralethal doses and sacrificed 2 and 48 hours later gave positive bioassays for leukemic cells.

Of great interest were findings of the effect of 4-amino-PGA and related compounds on a series of mouse and rat tumors[60,72,77]. Susceptible mice were inoculated with Sarcoma 180 and after 24 hours treatment was initiated with varying doses. During treatment with effective doses tumor growth was inhibited but was resumed as soon as therapy ceased. When the administration of antifolic compounds was delayed for more than 24 hours after tumor implantation, the inhibitory effect of treatment became progressively weaker and was hardly noticeable after 7 days delay. The materials were found to be rather toxic to mice and the range between tumor dose and lethal dose was narrow. Doses effective against tumor growth also depleted normal erythropoiesis in bone morrow[85]. Of the agents tried, 4-amino-N_{10}-methyl-PGA provided the most favorable range of therapeutic activity.

Further studies with 6 other mouse and 2 rat tumors using a similar technic, but giving the tumors in rats a 6

day start, were very illuminating[77,80b]. The investigators found marked inhibition of the Patterson lymphosarcoma in mice and of the reticulum cell sarcoma, R39, in rats. Sarcoma R39 appeared to be so sensitive that on several occasions bioassays in rats were negative with tumor material from treated animals. These experiments provided a spectrum of reaction of experimental tumors according to their susceptibility to the antifolic compounds. The effective tumor doses in the rats were quite toxic; many died with depletion of the marrow and intestinal lesions. The mammary adenocarcinoma, E0771, and the Harding-Passey melanoma in mice showed only a slight inhibition. The Wagner osteogenic sarcoma in mice characterized by a high alkaline phosphatase as well as the Flexner-Jobling carcinoma in rats showed no inhibition whatsoever.

According to the above findings the 4-amino-folic acids prevent the development of Rous sarcoma in New Hampshire Red baby chicks and in a few cases cure the rat sarcoma, R39. The effect on a few other susceptible tumors is only growth-inhibition but never curative and to obtain this action the compounds have to be given shortly after tumor implantation. The results clearly indicate that a great variety of susceptible and resistant tumors exists.

Effect of 4-Amino-PGA and Related Antagonists in Human Cancer. The early reports of the use of folic acid antagonists in the treatment of human leukemia created much interest. After it had been observed that 3 cases of chronic myeloid leukemia rapidly relapsed under treatment with PGA and improved on withdrawal of the vitamin, a crude antagonist, "X-methyl folic acid," was employed in one further case[33]. A remission resulted after 100 days of treatment. On withdrawal of the antagonist the leukemia relapsed. A second remission had begun following renewed treatment with the antagonist when the patient died.

About the same time investigations were in progress employing the first of the series of 4-amino-analogs, namely, 4-amino-PGA or aminopterin. Later members of the series include 4-amino-N_{10}-methyl-PGA or amethopterin and 4-amino-PAA or amino-an-fol. Farber, Diamond, *et al.*, were the first to report preliminary studies with aminopterin in 16 children with acute leukemia[20]. Various degrees of temporary improvement occurred during therapy in 10 cases. Details of laboratory studies and clinical findings were given of 5 cases. Six failed to respond and 4 of these were dead at the time of reporting. Spleen, liver and lymph nodes decreased in size and a marked effect on the leukemic bone marrow with decrease of immature cells in the peripheral blood was noted in responsive cases. Hemoglobin and platelets tended to return to normal. Studies on bone morrow showed changes varying from a decrease to a disappearance of leukemic cells. A wide range of general hypoplasia of the marrow with erythrocyte precursors and megaloblasts was seen. Further toxic manifestations of the drug such as stomatitis with ulceration occurred, and crude liver as well as PGA and conjugates were given to forestall them. Blood transfusions and antibiotics were also given as supporting therapy whenever necessary.

In a later paper Farber[21] reported remission in cases of Hodgkin's disease, lymphosarcoma, and neuroblastoma, exact details of which have not yet been published. Also reported were results of 60 children with acute leukemia treated with aminopterin, amethopterin, or amino-an-fol. Clinical and hematological improvement were claimed in about 50% of these

cases, which have not yet been described in detail. The effective daily doses used were 0.5 to 1.0 mg. for aminopterin, 3 to 5 mg. for amethopterin, and 25 to 50 mg. for amino-anfol. In this group stomatitis, ulceration of mouth and tongue, pharyngitis, atrophic changes in the intestinal epithelium, diarrhea and intestinal hemorrhage, and depletion of the marrow leading to aplasia were noted. Efforts to counteract these effects with liver extract, vitamin B-complex and folic acid, were only partially successful. Suspension of administration of antagonists for 4 to 7 days appeared to be more effective.

Farber introduced an arbitrary minimum of 3 weeks of life of an acute leukemia while under treatment with antifolic compounds as basis for admission of the case to his statistics. During this period the patients most severely ill will have died or the antifolic therapy given will have had an opportunity to affect the disease. This arbitrary selection might explain in part the high proportion of remissions claimed for antifolic therapy. The remissions reported were temporary in all instances though 2 children were alive after about 2 years.

Subsequent investigators, using approximately the same doses of 4-amino-PGA and its analogs in the treatment of leukemia and cancer, encountered often the toxic symptoms described by Farber. Attempts to prevent or treat these lesions with liver extract or folic acid failed and treatment had to be interrupted or abandoned for this reason. Furthermore, no definite pattern of treatment with the 4-amino-folic acids has yet emerged. Treatment is adjusted to the individual tolerance, and requirement varies from case to case. Some investigators have treated until tumor remissions occurred and then continued with a maintenance therapy. Others have given several separate courses of treatment with intervals when severe marrow changes or tumor remissions occurred.

Additional studies by other workers using similar doses of the 4-amino-folic acid antagonists in the treatment of acute leukemia of childhood revealed further information. Guest[31] had the best results with 7 remissions in 10 consecutive cases. Other authors reported lower incidences of remissions. Meyer[57] saw 4 remissions in 18 cases., Burchenal[9], 3 in 19 cases, Pierce[71], 5 in 9 cases, Stickney[76], a few in 18 cases, and Kracke[46], slight improvements in 14 of 29 cases. But Neligh *et al.*[61] saw no effect on the clinical course.

In adults with acute leukemia Meyer[57] saw 3 temporary remissions in 20 cases, Dameshek[13], 9 in 31 cases, Burchenal *et al.*[9], 2 in 12 cases, and other workers[39], only occasional improvement.

According to the figures at hand, a total of about 250 cases of acute leukemia in man have been treated with the 4-amino-folic acids with temporary remissions in about 30%. The remissions typically lasted from several weeks to a few months. In some instances several remissions were observed in the same case; but no cure was claimed by any investigator.

In chronic lymphoid leukemia a decrease in immature lymphoblasts and an occasional slight decrease in the size of enlarged lymph nodes but no real remissions were noted[3,9,57,61]. In chronic myeloid leukemia a decrease in total leukocyte count and decrease of the primitive elements with an increase of the more mature forms and a transitory slight decrease of enlarged spleens were noted. However, no remissions occurred comparable to the ones seen in cases of acute leukemia. The erythropoiesis showed in both forms of chronic leukemia marked

depletion and became partly megaloblastic[3,87].

Other workers [9,84] studied the effects of the 4-amino-folic acids in 40 human cancers. In adults they observed regression of metastasis of 2 cases of breast carcinoma and decrease of the size of a seminoma. In children[9] two cases of lymphosarcoma and 1 case of reticulum cell sarcoma showed temporary remissions. But other cases of lymphosarcoma, Hodgkin's disease, mycosis fungoides, multiple myeloma, neuroblastoma, osteogenic sarcoma, Ewing's sarcoma, cancer of the lung, bladder, stomach, female breast, ovary, sarcoma of the jaw and melanocarcinoma failed to respond.

From the above it is evident that the 4-amino-folic-acid antagonists have a definite action on erythropoiesis, myelopoiesis, and lymphopoiesis in man. The best therapeutic effects so far obtained in cancer of man are repeated temporary remissions of acute leukemia in children and adults.

Comment. The evaluation of the effect of the 4-amino-folic acids on the acute leukemias in man is difficult. Unlike the situation in animal experiments with controls and repeatable, well-defined conditions, the diagnosis as well as the course of the disease is variable. According to Diamond (quoted from Farber[21]) in children with acute leukemia spontaneous remissions occur in 10% of all cases. Spontaneous remissions in adults have also been described with an emphatic warning not to forget this fact[37,38]. Furthermore, the diagnosis of acute leukemia is based on the time of death and sometimes cases diagnosed as acute have become subacute or chronic. The increased care of patients with antibiotics, blood transfusions, and hemostatics and the intense study of the cases under treatment introduce factors not included in previous statistics. However this may be, it is the impression of some investigators that the compounds have a definite effect on the acute leukemic process as reflected in a remission rate never seen before.

One must look forward to future research to explain why only a fraction of the acute leukemias respond to treatment and chronic cases respond so rarely; why in some cases relapses are seen under maintenance therapy with the 4-amino-folic acids; and why in other cases remissions occur following therapeutic attempts when liver and folic acid are given to palliate toxic manifestations.

Experimental work in chickens measuring folic acid requirements of different tissues is of great interest in this connection[7,11,27,63,66]. It has been shown in birds that general growth, growth of feathers, pigmentation, erythropoiesis, and myelopoiesis can be selectively inhibited by varying grades of folic acid deprivation. Such results indicate that growing tissues of the normal organism vary significantly in their needs for folic acid. This can be expected to hold for neoplastic tissues. These experiments might be an indicator for future work to measure the folic acid requirements of tumor cells and for tumor growth and thus to explain varying response of neoplastic tissues to folic acid antagonists.

ADDENDUM

Since writing this review, additional information has been received by personal communication. Silverman found regression of leukemic skeletal lesions and the occurrence of heavy transverse bands of increased density at the ends of shafts of long bones in 7 children treated with aminopterin (to be presented before the Society for Pediatric Research, Atlantic City, June 1949). L. Meyer[57] augmented his observations with 8 patients with acute leukemia treated with amino-an-fol without apparent effect. C. H. Smith treated with aminopterin 10 children who had acute leukemia. He observed reductions of blast forms in the marrow in some instances and, in one child, a transitory increase in normoblasts but no true remission.

M. Wintrobe treated 10 patients with acute leukemia with aminopterin and noted a distinct remission in one adult lasting for about 6 months. Two children at present under treatment are doing reasonably well.

J. H. Dale's statistics of the course of acute leukemia in children (J. Radiol., 1949, in press) are of special interest and may serve to assess the effectiveness of chemotherapeutic procedures on the basis of time of survival. Of 72 cases of leukemia in children observed during the period from September 1932 to June 1948, 39 had a complete follow-up. Thirty-six of the cases exhibited clinical manifestations of "acute" leukemia and showed a predominance of blast forms. Twenty-seven (75%) of the 38 cases died within 6 months of onset of the disease, 8 cases (22%) died between 6 months and one year, and one case died after 14 months. These results illustrate the variable course of "acute" leukemia. An even higher percentage might have been expected to survive for longer than 6 months had antibiotics been available during the whole period of the recorded observations. It is against the background of the natural course of the disease and of effects of supportive therapy in the form of blood transfusions and antibiotics that therapeutic claims have to be evaluated.

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PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF FEBRUARY 15, 1949

Blood Temperature in the Heart and Blood Vessels of the Dog. STEVEN M. HORVATH, M.S., Ph.D., E. L. FOLTZ, M.D., A. RUBIN, M.D., and B. K. HUTT, P. T. (Dept. of Physical Medicine, Graduate School of Medicine, and the Dept. of Pharmacology, School of Medicine, Univ. of Penna.). Temperatures of the blood, tissues, skin and rectum in anesthetized dogs have been determined. Cournand type catheters with thermocouples at the tip were placed roentgenoscopically in the coronary sinus and the right ventricle or pulmonary artery. These catheters were also used to measure temperature in other areas of the body. Smaller catheters were similarly inserted into the femoral artery and vein. The emf developed by the thermocouple was measured with a type K-2 Leeds and Northrup potentiometer.

The vascular temperatures obtained indicate clearly that the concept of a uniform body temperature is erroneous. The temperature varies widely and is dependent on activity of the organs and the environmental temperature. Since morphine-nembutal anesthesia has a tendency to lower body temperature, it was possible to study the temperature gradients at different rectal temperatures. The following table presents some of the mean temperatures and gradients obtained in 19 experiments on 11 animals.

The work of the heart was altered with intravenous injections of epinephrine, aminophylline and methedrine and with inhalations of amyl nitrite. The temperature of the blood in the right heart and coronary sinus during the action of drugs was determined. These data were discussed in relation to the effect of these drugs on cardiac work and cardiac efficiency.

Location of Catheter	°F.
Rt. Ventricle	98.7
Pulmonary Artery	98.7
Coronary Sinus	98.9
Femoral Artery	98.3
Femoral Vein	96.6
Muscle, Thigh	97.6
Subcutaneous, Thigh	96.5
Skin, Thigh	92.1
Rectum	99.1

The Effect of Intravenous Aminophylline upon Cardiac Oxygen Supply and Demand. E. L. FOLTZ, M.D., A. RUBIN, M.D., and W. A. STEIGER, M.D. (Dept. of Pharmacology, Univ. of Penna., and Division of Cardiology, Philadelphia General Hosp.). Changes in the coronary arteriovenous oxygen difference were studied in 14 normal, intact dogs under morphine-nembutal anesthesia. Arterial blood was obtained by femoral artery puncture while coronary venous blood was sampled from the coronary sinus through a catheter which was introduced under fluoroscopic guidance (Am. J. Physiol., **152,** 341, 1948). Simultaneous arterial and coronary venous samples were collected before and after the intravenous injection of either saline or aminophylline solution.

Coronary venous oxygen saturation fell during a period from 4 to 8 minutes after injection of aminophylline; the mean values for saturation decreased from 30.2% to 17.7%, and the unsaturation (Cor. A-V difference) rose from 62.1% to 74.1%. Compared with data of saline control experiments, the dif-

ferences are significant. No measurable change was noted in mean arterial blood pressure; mean pulse rate increased from 145 to 165 beats per minute. Electrocardiographic record revealed no significant change in pattern as a result of catheterization, experimental procedures, or drug injections.

Previous studies have demonstrated that aminophylline dilates the coronary vessels but also stimulates the heart to contract more vigorously with resulting increases in cardiac output and cardiac work; the observed changes in coronary venous oxygen saturation indicate that the stimulating effect of aminophylline increases cardiac oxygen consumption more than the coronary vasodilating action augments coronary flow and the delivery of oxygen. The result is the production or intensification of myocardial anoxia.

Inhibition of the Knee Jerk from Tendon Spindles of Crureus. G. P. McCouch, M.D., I. D. Deering, M.S., W. B. Stewart, M.D., and W. W. Chambers, Ph.D (Depts. of Physiology and Anatomy, Univ. of Penna.). In decerebrate cats the tension of quadriceps and the action potential of rectus and crureus were isometrically recorded. The knee jerk was elicited by a mechanical tapper, which stretched the muscle by raising the lever shank. Conditioning volleys, not significantly above threshold for contraction, were delivered through bare needles of which one passed through the patellar ligament, the other transversely through vastocrureus a few millimeters proximal to the tendon of crureus.

Inhibition curves may be preceded by facilitation at intervals between conditioning and test stimuli up to 2 m. sec. This is followed by a descending limb, which reaches maximal depth within 8 or 9 m. sec. Total duration of inhibition is variable, being greater with more proximal positions of the muscle electrode, which involve more receptors, than with distal positions which engage fewer end organs. It ranges from 20 to 100 m. sec. With 4 electrodes, one in the patellar ligament and 3 in crureus approximately 10, 21, and 29 mm. from the distal end of the muscle, curves were run conditioning from each adjacent pair. Inhibition was deep from the distal, slight from the middle, and virtually absent from the proximal pair.

Two factors may be postulated to account for the shape of the curve. The first is facilitation from the inevitable involvement of muscle spindles. The second results from the multisynaptic character of the inhibitory arc and its consequent afterdischarge.

Intermediary Metabolism of Phenylalanine Labeled with C^{14}. Bernard Schepartz, Ph.D.,* and Samuel Gurin, Ph.D. (Dept. Physiol. Chem., Univ. of Penna.). Administration of DL-phenylalanine (labeled in the carboxyl and alpha positions) to phlorhizinized rats results in the appearance of C^{14} in the urinary ketone bodies as well as in the respiratory CO_2. Upon incubation of this type of phenylalanine with liver slices, acetoacetate labeled solely in the carboxyl group is obtained.

When ring-labeled phenylalanine (carbons 1, 3, 5) is administered to phlorhizinized rats, C^{14} appears in the respiratory CO_2 as well as in the acetone moiety of the urinary acetoacetate. Incubation of ring-labeled phenylalanine with liver slices produces acetoacetate labeled chiefly in the terminal methyl group.

The aromatic ring of phenylalanine readily undergoes cleavage in the course of metabolism, the immediate precursor of acetoacetate being a four-carbon unit derived from the ring and side-chain. Apparently no two-carbon units are involved in this pathway.

It is apparent that the alpha carbon

of phenylalanine becomes the carboxyl carbon of acetoacetate, while either carbon atom 1 or 3 of the ring forms the terminal carbon of acetoacetate. This furnishes direct proof that the side-chain of phenylalanine shifts to an adjacent ring carbon prior to the formation of ketone bodies.

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BOOK REVIEWS AND NOTICES

DISEASES OF THE FUNDUS OCULI WITH ATLAS. By ADALBERT FUCHS, M.D., e.o. Prof. of Ophthalmology, Univ. of Vienna. Translated by ERIC PRESSBURGER, M.D., Edited by ABRAHAM SCHLOSSMAN, M.D. Pp. 337; 322 ills., 241 in color. Phila.: Blakiston, 1949. Price, $30.00.

THIS beautifully illustrated text on diseases of the ocular fundus is the first English edition of the author's well known book in German. It is greatly to the credit of the American publishers that they have undertaken this edition, which is limited to slightly less than 1000 copies. The text has exceptional value because of the author's long experience in the histopathology of the eye. As a result, he is able to correlate the ophthalmoscopically visible changes with the histological picture; a unique feature of the book is the publication of plates illustrating the histopathology along with the fundus picture.

The translation is excellent and, unlike so many translations, particularly those from the German, is in good English style with short, readable sentences. Some of this credit must also go to the editor.

The book is divided into the usual sections on the appearance of the normal fundus, congenital anomalies and then diseases of the various anatomical parts of the eye, such as the optic nerve, retina and choroid. Special chapters on certain diseases of the eye, such as glaucoma, tuberculosis, syphilis, tumors and detachment of the retina follow.

While the plates are still not as good as those of the early German and English atlases, they are the best that have appeared in recent years in any language, particularly in English. In spite of its cost, this book should be bought by all who have a serious interest in the ophthalmoscopic changes in local and general diseases.

F. A.

CLINICAL ASPECTS AND TREATMENT OF SURGICAL INFECTIONS. By FRANK LAMONT MELENEY, M.D., F.A.C.S., Assoc. Prof. of Clinical Surgery, College of Physicians and Surgeons, Columbia Univ. Two vols. Pp. 840; 287 ills. Phila.: W. B. Saunders, 1949. Price, $12.00.

THIS is a companion volume to "Treatise on Surgical Infections" (Oxford University Press, 1948), by the same author. These two volumes present a timely and comprehensive review of the fundamental and practical aspects of the prevention, recognition and treatment of surgical infections.

The first chapter of "Clinical Aspects" stresses the practical importance of correlating bacteriological studies with a knowledge of immunology and the physiology of inflammation and tissue repair. Excellent reviews of past and current literature dealing with each type of infection are included. The subjects are liberally supplemented with illustrative case histories from the author's extensive experience. As the case histories represent not only patients treated with antibiotics but patients treated when only sulfonamides were available, and some patients treated before sulfonamides were available, the histories demonstrate well the modern trend in chemotherapy.

H. Z.

OBSTETRIC ANALGESIA AND ANESTHESIA. By FRANKLIN F. SNYDER, M.D. Assoc. Prof. of Obstet. and Anat., Harvard Med. School. Pp. 401; 114 figs. Phila.: W. B. Saunders, 1949. Price, $6.50.

THE title of this volume is misleading. It should not be regarded as a text on obstetric anesthesia because of the scant coverage afforded such topics as the use of spinal anesthesia in obstetrics. The book, however, represents a significant contribution to the field of neonatal physiology. The author has done considerable fundamental work on "Respiratory Injuries to the Child" which he presents in the first section (188 pages). This alone makes the monograph of value. It is unfortunate that the summaries of each chapter are so detailed and lengthy, and this detracts from reader interest.

R. D.

THE STORY OF SCABIES. By REUBEN FRIEDMAN, M.D., Assoc. Prof. of Dermatology, Temple Univ. School of Medicine. Vol. 1. Pp. 468; 114 ills. New York: Froben Press, 1948. Price, $7.50.

THIS is the first volume of a projected series of 4 dealing with all aspects of "The Story of Scabies." When completed, these

books will culminate Dr. Friedman's protracted efforts to collect all that is known and some things that are unknown about this interesting and widely prevalent parasitosis.

The first volume unites in revised form 2 of the author's previously published works ("Scabies—Civil and Military" (1941) and "Biology of Acarus Scabei" (1942)). It deals with scabies from the earliest times to the beginning of America's participation as an active belligerent in World War II. Volume 2 will contain the advances made from the beginning of World War II until the end of 1947. Volume 3 will be devoted to the history of scabies, and Volume 4 will contain chiefly translations of certain classical contributions to our knowledge of scabies.

Written by one of the world's foremost authorities on scabies, this volume meets the reviewer's most critical expectations. Nothing of importance has been omitted. It is beautifully illustrated and well written. It has appeal both for the medical historian and the clinician.

H. B.

HANDBOOK OF DISEASES OF THE SKIN. By RICHARD L. SUTTON, M.D., and RICHARD L. SUTTON, JR., M.D., Univ. of Kansas Medical School. Pp. 749; 1057 ills. St. Louis: C. V. Mosby, 1949. Price, $12.50.

THE Suttons have achieved brevity and practicality in their production of a new text for medical students, practitioners and specialists in dermatology. Although this Handbook is a small volume, it contains more useful, well presented, well documented and well illustrated material than many texts twice its size. It is, however, not a mere catalog of the views of various contributors to the subject but contains many original personal views, especially the technic in contact dermatitis of relieving the patient by elimination of all possible causes, then identifying the actual cause by systematic increment of the patient's chemical environment. Acne vulgaris and urticaria are also treated by the authors' special technics. The 1057 illustrations are well chosen; especially notable are those dealing with the normal adult and fetal skin. The text itself is well written and with adequate detail. Some sections are superbly handled. It is presented in a logical order and with good correlation of the cutaneous manifestations with general medicine and biology. There are surprisingly few typographical errors in this book.

The difficult matter of references to the literature is handled in novel fashion by placing references parenthetically as near the material cited as possible. This is somewhat disturbing to the average reader, but is more so to the experienced worker, because as a space-saving device the authors have still further abbreviated the already abbreviated names of the medical journals referred to. The reviewer hopes that, if possible, some less distracting method will be considered for future editions.

The Suttons have produced another creditable aid to the understanding of dermatology. It deserves wide acceptance.

H. B.

BLOOD TRANSFUSION. By ELMER L. DEGOWIN, M.D., Assoc. Prof. of Internal Medicine, ROBERT C. HARDIN, M.D., Ass't Prof. of Internal Medicine, State Univ. of Iowa, and JOHN B. ALSEVER, M.D., Senior Surgeon U. S. Pub. Health Service. Pp. 587; 200 ills. Philadelphia: W. B. Saunders, 1949. Price, $9.00.

ALTHOUGH good books dealing with the problems of blood transfusion are available, a new one of this calibre is welcome. Its authors have had extensive experience in the field of transfusion therapy and have made, individually and as a group, original contributions of considerable importance. Their book is clearly and simply written. All important problems which confront the personnel of a transfusion service are discussed. The chapter on laboratory procedures is of unusual value because of its simplicity, detail, and ingenious illustrations. This book is highly recommended to all who are interested in the transfusion of blood and blood derivatives, from technicians to experts.

C. K.

SURGERY OF THE EYE. By MEYER WIENER, M.D., Emeritus Prof. of Clinical Ophthalmology, Washington Univ. School of Medicine, 2d ed. Pp. 426; 425 ills. New York: Grune & Stratton, 1949. Price, $12.00.

THIS 2d edition has been badly needed. It possesses the advantages of being reasonably short and the material is presented in a lucid and concise manner. The illustrations are up to the standard set in the 1st edition.

Those procedures that have been useful to the author are described with the variations in technique which he employs. Some of the newer operations, such as the Burch implant and evisceration and goniotomy are included. Procedures still regarded as experimental in nature, such as the various types of exposed implant following enucleation, are omitted. The author describes his punch technique for keratoplasty which this reviewer believes

might be dangerous, due to the danger of iris prolapse.

H. S.

ATLAS OF PERIPHERAL NERVE INJURIES. By WILLIAM R. LYONS, Ph.D., Assoc. Prof. of Anatomy, Univ. of California Medical School, and BARNES WOODHALL, M.D., Prof. of Neurosurgery, Duke Medical School. Pp. 339; 135 ills., 15 in color. Phila.: W. B. Saunders, 1949. Price, $16.00.

UPON 135 large size plates, 15 of them in color, this book furnishes complete documentary evidence of the pathological changes in proximal and distal stumps of severed nerves, of nerve lesions in continuity as found in resected parts of the injured nerve, of the consequence of various types of sutures which proved unsatisfactory and had to be removed, and of several kinds of grafts. Each chapter is preceded by a clear summary of the findings, beginning with the structure of the normal nerve. The microphotographs and the accompanying legends are excellent and show distinctly the various sheaths of the nerve and their cells in normal and pathological conditions. Instructive photographs of skin scars, Roentgen-ray pictures of fractures and bone deformities, examples of the gross appearance of nerves and their operative repair and of the pathological specimen and the miscroscopic changes under low and high power, together with the comprehensive clinical and pathological description, give a vivid picture of the processes at different time intervals following nerve injuries.

The book is indispensable for the neurosurgeon and the neuropathologist, for the general pathologist who is concerned with nerve injuries in industry or war, and for most neurologists. It will remain a standard book for years to come.

F. L.

NEW BOOKS

Atlas of Neuropathology. By WILLIAM BLACKWOOD, Ass't Pathologist, Nat. Hosp., Queen's Square, London, T. C. DODDS, Lecturer, Society of Radiographers, Scottish Branch, and J. C. SOMMERVILLE, Univ. of Edinburgh. Pp. 199; 262 ills. Balt.: Williams & Wilkins, 1949. Price, $9.00.

This small atlas should prove of considerable value to those whose work brings them into occassional contact with neuropathology. It is brief and selects only the highlights of each lesion presented, and for that reason might be of less value to the full-time neuropathologist. The range of subjects covered is broad, but the salient features of each subject are clearly brought out; no space is wasted on ramifications which are not strictly within the field of neuropathology. The illustrations are well chosen and technically excellent. The reviewer recommends the book highly. A. R.

Clinical Orthoptics. By MARY EVERIST KRAMER. Edited by ERNEST A. W. SHEPPARD, M.D., Prof. of Ophthalmology, George Washington Univ. School of Medicine, and LOUISA WELLS-KRAMER. Pp. 475; 147 ills. St. Louis: C. V. Mosby, 1949. Price, $8.00.

This is one of the first texts on orthoptics to come from this country, the previous standard texts having all been written in England. The work covers the various phases of knowledge which an orthoptic technician should acquire before presenting herself to the American Board of Orthoptics for examination. The anatomy and physiology of the eye are given adequate consideration. The main portion of the book deals with the treatment of the various forms of strabismus by means of orthoptics.

The book is highly recommended for all those who are interested in the subject of strabismus.

F. A.

Child Health. Edited by ALAN MONCRIEFF, Nuffield Professor of Child Health, University of London, and WILLIAM A. R. THOMSON, Pp. 254. London: Eyre and Spottiswoode, 1947. Price, 14s.

THIS "Practitioner Handbook" is an expository presentation, with chapters contributed by many authorities, describing for general practitioners the new English system of the numerous organized child health services. There are chapters on Child Welfare Centers, School Health Services, Day Nurseries, Schools for Crippled Children, and so forth. There are also several chapters on nutrition, feeding, and prevention of certain diseases. The American pediatrician will find much information of usefulness in these pages, despite the fact that the text is slanted to the problems of another country. I. W.

Facts About Nursing, 1948. By AMERICAN NURSES' ASSOCIATION. Pp. 106. New York: A. N. A., 1790 Broadway, 1949. Price, 35c.

"THE first authoritative survey since the war among U. S. nurses."

Diabetic Menus, Meals and Recipes. By BETTY M. WEST. Introduction by RUSSEL F. RYPINS, M.D. Pp. 254. New York: Doubleday, 1949. Price, $2.95.

The Psychoanalytic Reader. Edited by ROBERT FLIESS, M. D. Vol. 1. Pp. 392. New York: International Universities Press, 1949. Price, $7.50.

"THE contributions united here have been gathered by scanning the complete literature of the field, from the oldest Viennese *Jahrbach fur Psychoanalyse*, founded in 1909, to the British and American psychoanalytic periodicals of today . . . What appears most profitable of this literature will be published in the Reader's several volumes, of which the present one is the first . . . "

Social Medicine, Its Derivations and Objectives. Edited by IAGO GALDSTON, M. D. The New York Academy of Medicine Institute on Social Medicine. Pp. 294. New

York: Commonwealth Fund, 1949. Price, $2.75.

In this study of the origins and aims of Social Medicine, the contributions of the 26 well known participants are arranged in 7 groups. The first 2, of a more general nature, are on the relation of medicine to society and the relation of social medicine to clinical and preventive medicine. The other 5 treat special aspects such as the place in social medicine of epidemiology, nutrition, psychiatry. This is a worthy and valuable statement of current thought on a highly important subject that has not hitherto received sufficient attention by the medical profession in this country. E. K.

Medical Clinics of North America. Chicago Number. *Diseases of the Skin.* Pp. 292; 135 ills. Phila.: W. B. Saunders, January, 1949. Price, $15.00 a year.

The wide coverage of this well organized and composed symposium is indicated by a list of the subjects discussed, which include: neurodermatitis, dermatomyositis, sarcoidosis, scleroderma, disseminated lupus erythematosus, changes in the nail from the use of "base coats," tumors of the skin, exfoliative dermatitis, herpes, pemphigus, cutaneous allergy, eruptions due to food, cutaneous tuberculosis of the Negro, dermatological therapy and dermatopathology. H. B.

Cancer of the Esophagus and Gastric Cardia Edited by George T. Pack, M.D., Clinical Prof. of Surgery, New York Medical College. Pp. 192; 65 ills. St. Louis: C. V. Mosby, 1949. Price, $5.00.

The 11 papers of this specially bound volume of the June 1948 issue of "Surgery" are written by men outstanding in the recent developments in this field. The book affords an excellent summary of American surgical practice in relation to this disease. J. J.

Collateral Circulation (Anatomical Aspects). By Daniel P. Quiring, Ph.D., Assoc. Prof. of Biology, Western Reserve Univ. Pp. 142; 61 ills., 46 in color. Phila.: Lea & Febiger, 1949. Price, $5.00.

This compact presentation, by description and diagram, of the major cross connections and side channels of arteries and veins has obvious values for the internist and surgeon as well as the anatomist and physiologist. Five of the 8 chapters deal with the collateral circulation of a given body region, involving such important problems as results of occlusion of cerebral, acoustic, coronary arteries, and others, and with the benefits that may be brought by collateral circulations. Venous collateral circulation with a different set of problems is considered in each section, the book closing with a suggestive illustration of Beck's experimental revascularization of the dog's heart.

This correlation by an anatomist of gross structure with clinical problems should find welcome space on many shelves. E.K.

NEW EDITIONS

Surgical Technique and Principles of Operative Surgery. By A. V. Partipilo, M.D., F.A.C.S., Assoc. Clinical Prof. of Surgery, Loyola Univ. 4th ed. Pp. 676; 997 ills. Phila.: Lea & Febiger, 1949. Price, $15.00.

This 4th edition is the 1st to be published by Lea & Febiger. The book is well illustrated and well printed. A consistent editorial plan has not been followed in regard to references and questionnaires: certain chapters have good bibliographies following them, some have none; certain chapters are followed by rather elementary questionnaires, some are not. The reason for this lack of uniform policy is not clear.

While the Reviewer does not agree with a number of procedures advocated by the authors and thinks that if physiologic considerations are discussed at all they should be given greater attention, he would recommend this book to the young surgeon for a review of operative procedure. I. R.

The Mentally Ill in America. By Albert Deutsch. 2d ed. Pp. 555; 8 ills. New York: Columbia Univ. Press, 1949. Price, $5.50.

The 2d edition of this worth while book includes additions and revisions, such as a new chapter entitled "Psychiatry in World War II" and a completely revised chapter on modern trends in institutional care and treatment. The book is directed toward the general reader as well as the physician. W. P.

Child Psychiatry. By Leo Kanner, M.D., Assoc. Prof. of Psychiatry and Pediatrics, Johns Hopkins Univ. 2d. ed. Pp. 752. Springfield, Ill.: Charles C Thomas, 1949. Price, $8.50.

This new edition of a comprehensive and valuable text published 13 years after the appearance of the 1st edition will be welcomed by pediatricians, psychiatrists, and others. Extensive revisions and additions have been made that give greater clarity and depth to the work. W. P.

Human Embryology and Morphology. By Sir Arthur Keith. 6th ed. Pp. 690; 578 ills. Balt.: Williams & Wilkins, 1948. Price, $10.00.

This new edition presents numerous improvements. Chapters on the development of the urogenital system and limb evolution have been added. There are numerous new illustrations. Recent factual material and references are included. The chapter on experimental embryology seems inadequate, considering how profitable has been this field of investigation. The occasional use of strained analogies often confuse the understanding of the facts presented. This edition is an excellent reference text for morphological changes occurring during embryogenesis. I. Z.

Manual of Clinical Laboratory Methods. By Opal E. Hepler, Ph.D., M. D., Assoc. Prof. of Pathology, Northwestern Univ. Medical School. 4th ed. Pp. 387; 36 figs., 8 color plates. Springfield, Ill.: Charles C Thomas, 1949. Price, $8.50.

The Business Side of Medical Practice. By Theodore Wiprud. 2d ed. Pp. 232; 22 figs. Phila.: W. B. Saunders, 1949. Price, $3.50.